FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Meeting of the Psychopharmacologic Drugs Advisory Committee
FDA White Oak Campus, 10903 New Hampshire Ave,
Bldg. 31, Conference Center, Silver Spring, MD

September 16, 2010

Background Materials

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Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Addiction Products

MEMORANDUM

DATE: August 12, 2010

FROM: Bob A. Rappaport, Division Director
Division of Anesthesia, Analgesia, and Addiction Products

TO: Chair, Members, and Invited Guests, Psychopharmacologic Drugs Advisory Committee (PDAC)

RE: Overview of the September 16, 2010 PDAC Meeting to Discuss Efficacy Supplement to NDA 21-897 for Vivitrol (naltrexone for extended-release injectable suspension) for prevention of relapse in recently-detoxified opioid dependent patients

At this meeting of the Psychiatric Drugs Advisory Committee, we will be discussing a supplemental application for the new drug application (NDA) 21-897, for Vivitrol (naltrexone for extended-release injectable suspension), submitted by Alkermes, Inc., to add a new indication for use in treatment of opioid dependence.

During this meeting, representatives from the Agency and the applicant, Alkermes, Inc., will present:

- Data from the clinical trial performed to assess the safety and efficacy of Vivitrol in the treatment of opioid-dependent patients. While the study design (randomized, placebo-controlled, parallel group study of 6-months duration) is not novel, some of the analytic approaches and concepts are. Furthermore, the application is supported by a single efficacy trial conducted outside the U.S.
- Observations from the inspections of the clinical sites by the FDA's Division of Scientific Investigations
- A discussion of the role of cultural and ethnic factors in interpretation of foreign clinical trial data

Following these presentations, you will be asked to assess these findings and to discuss the adequacy of the data to support expanded use of Vivitrol into the opioid-dependent population.

We will ask the committee to address whether the available efficacy data--a single placebo-controlled efficacy trial taken together with pharmacodynamic data showing that Vivitrol blocks the effects of exogenously administered opioids--are sufficient to conclude that the drug is effective for the intended use.

We will ask the committee to address whether the cultural and societal differences, the differences in the medical care system and the available treatment alternatives, or other differences between the studied population and the American target population creates a need for a "bridging study" of some type to provide assurance that the drug would be effective in the American population.

We will ask the committee to address whether there are indication-specific safety concerns that have not been adequately addressed by the existing safety data, and whether additional safety data may be needed in the American population.

The Division and the Agency are grateful to the members of the committee and our invited guests for taking time from your busy schedules to participate in this important meeting. Thank you in advance for your advice, which will aid us in making the most informed and appropriate decision possible.

Clinical Pharmacology of Vivitrol (NDA 21-897)

Data from six clinical pharmacology and biopharmaceutics studies was submitted to NDA 21-897 in 2005 to support use of Vivitrol for the treatment of alcohol dependence. The same clinical pharmacology data also support use of Vivitrol for the treatment of opioid dependence. The clinical pharmacology studies investigated the relative bioavailability and single dose pharmacokinetics (ALK21-001, -002), multiple dose pharmacokinetics (ALK21-005), pharmacokinetics in mild and moderate hepatic impairment (ALK21-009), dose-finding opiate challenge study in opiate users (ALK21-004), and safety study (ALK21-006). Data pooled from the clinical pharmacology studies was analyzed to determine effect of covariates (such as age, sex, body weight, race, and polysubstance dependency and markers of renal and hepatic function) using population pharmacokinetic approach (Report# ALK21-011). All of the above indicated studies were noted in clinical pharmacology review dated 11/25/2005. A brief summary of the clinical pharmacology information pertinent to current submission on Vivitrol for the treatment of opioid dependence is summarized in this document.

Vivitrol is an extended release microsphere-based formulation of naltrexone incorporated into a biodegradable matrix of polylactide-co-glycolide for intramuscular use. Based on *in vitro* studies, the drug release from the microsphere formulation is hypothesized to occur in three phases as described below:

- The initial release of a small quantity of drug at or near the surface occurs during the first day following exposure of the microspheres to an aqueous environment.
- The hydration phase occurs during the first week. Physical erosion of the microspheres begins and some subsurface drug is released.
- The sustained release phase constitutes the majority of the release profile both in terms of overall duration and quantity of drug released. The sustained release phase takes place from Week 2 until drug release is complete and is governed by polymer erosion.

1. PK Characteristics of Vivitrol

Pharmacokinetics of Vivitrol are dependent on the release of naltrexone from microspheres. After IM injection, the naltrexone plasma concentration time profile is characterized by a transient initial peak, which occurs approximately 2 hours after injection, followed by a second peak observed approximately 2 - 3 days later. Beginning approximately 14 days after dosing, concentrations slowly decline, with measurable levels noted up to one month.

Table: Pharmacokinetics of naltrexone following single oral administration of Revia or intramuscular injection of Vivitrol.

Pharmacokinetic Parameter	Oral naltrexone 50 mg N = 28	Vivitrol 380 mg IM N = 12
C_{max} (ng/mL)	10.64 (6.92)	12.90 (4.67)
t_{max} (days)	0.04 (0.02-0.08)	2.00 (1.50-2.00)
$AUC_{0-\infty}$ (ng*days/mL)	1.270 (0.591)	143.5 (29.3)
$t_{1/2}$ (days)	0.1611 (0.1065)	4.948 (1.255)

The proposed 380 mg dose of IM Vivitrol is approximately 1/3rd compared to oral naltrexone (50 mg QD for 28 days = 1400 mg over 28 days). However, the exposure to naltrexone (AUC_{0-28}) over 28 days following Vivitrol administration is approximately four-fold higher than that with oral naltrexone due to higher bioavailability.

Following IM administration of 380 mg IM Vivitrol, the plasma levels of 6β-naltrexol are ~ two-fold higher than naltrexone and the PK profile appears to be in parallel to naltrexone. This would indicate that 6β-naltrexol disposition is formation rate-dependent. Repeated administration of Vivitrol, once a month for four months, did not result in significant accumulation of naltrexone. Naltrexone elimination appears release rate-dependent as the elimination half life for the product is approximately 5 days; while oral naltrexone has a 5 hour half life (study # ALK21-005).

2. Dose-finding Study Results

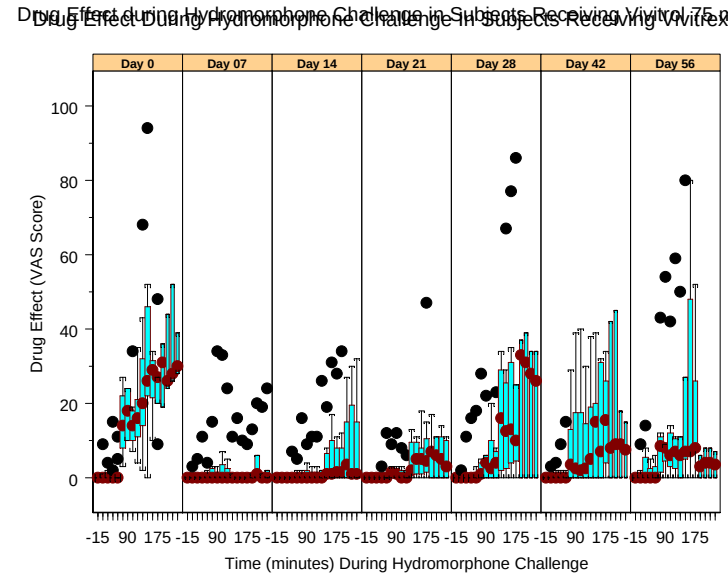
Pharmacodynamic data supporting clinical investigation of Vivitrol for the clinical trials in opioid dependence was derived from dose-finding study #ALK21-004. Specifically, evidence to support use of Vivitrol suspension dose, duration of action, dosing interval of was derived in terms of its opioid effect blockade.

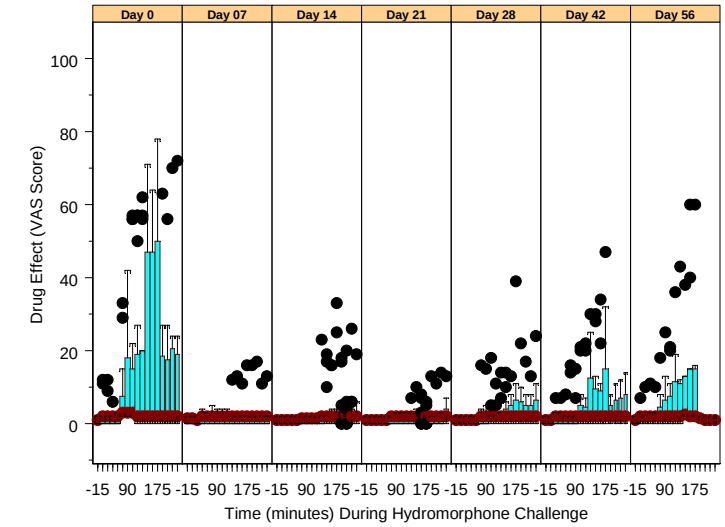
Study design: Study#ALK21-004 was a randomized, single dose opiate challenge study of Vivitrol suspension in non-dependent, opioid using adult subjects. Subjects were randomized in a 1:1:1 ratio to receive a single gluteal IM injection of Vivitrol suspension 75, 150, or 300 mg. A total of 28 subjects were recruited and 21 subjects finished the study.

Methods: Subjects were administered hydromorphone challenge, naloxone challenge and oral naltrexone tolerability assessment before study drug treatment. At Day 0, eligible subjects were administered the first dose of study drug. Experimental hydromorphone challenge sessions (to assess the level of opiate blockade) were conducted prior to and Days 7, 14, 21, 28, 42, and 56 after Vivitrol administration. Blood samples for measurement of naltrexone and 6β-naltrexol were obtained at screening and before hydromorphone/ placebo administration on Days 7, 14, 21, 28, 42, and 56.

Hydromorphone Challenge Test: Intramuscular hydromorphone injections were administered at 1-hour intervals at doses of 0 (placebo), 3, 4.5, and 6 mg. At a randomly selected evaluation visit, subjects received four 0 mg (placebo) doses at 1-hour intervals. The doses of hydromorphone utilized in this study seem appropriate considering its potency compared to heroin. Wallenstein S.L. et. al. (Pain (1990), 41: 5 -13) reported that following intramuscular administration hydromorphone is 5-times as potent as heroin on milligram basis with respect to analgesic activity, mood changes and sedation. Brands B. et. al. (Clin Pharm. Ther. (2004), 75(2): P3) indicate that IV, SC hydromorphone was 3 – 4 times more potent compared to heroin in terms of subjective measures in healthy casual injection heroin-users.

A variety of pharmacodynamic assessments were recorded 15 minutes before the first hydromorphone dose or placebo for hydromorphone dose and at 15, 30, 45 and 60 minutes after each dose. Pharmacodynamic effects are discussed with regard to the subjective measure of visual analog scale (VAS) response to question “Do you feel any drug effect?”





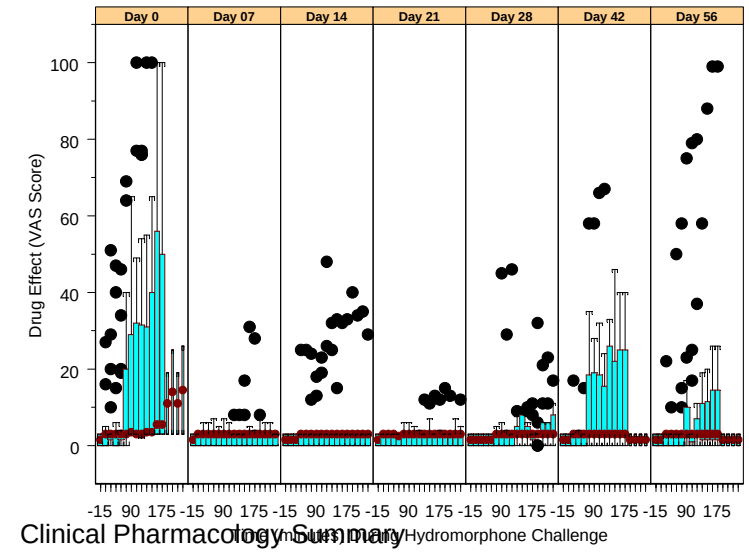


Figure Legend: Box-plot indicating VAS scores to the question "Do you feel any drug effect" administered during ~ 200 minutes of hydromorphone challenge test. Subjects received 75, 150 and 300 mg Vivitrol in parallel groups. The whiskers of the box plot include the data, the top of the box indicates 75th percentile, bottom of the box indicates 25th percentile, and solid brown circles indicate median, solid black circles indicate outlier observations.

Results:

Subjective VAS responses to the question, "Do you feel any drug effect?"

At screening or Day 0, during hydromorphone challenge test, a dose-related increase in drug effect was reported by all subjects.

At Day 7, the first post-dose assessment period following Vivitrol IM injection, complete opioid effect blockade was noted in all dose groups. A sustained blockade of opioid effects was noted for all doses at Day 14 upon administration of hydromorphone challenge. While recovery of opioid effects was noted in several subjects receiving 75 mg dose, subjects in the 150 mg and 300 mg dose groups had opioid effects blocked up to Day 28.

More number of subjects had opioid effect blockade beyond 28 days when receiving 150 mg and 300 mg dose of Vivitrol. Most number (83%) of subjects receiving 300 mg dose of Vivitrol were able to receive and tolerate 6 mg hydromorphone during the challenge test on Day 28.

In general, observations with objective measure data using pupillometry as the endpoint confirmed the observations made above. PK-PD analysis with pupillometry data suggested that naltrexone levels maintained above 1 ng/mL would block opioid effects of hydromorphone. On Day 28, 42% of subjects receiving 300 mg Vivitrol had plasma levels above 1 ng/mL. However, none of the subjects receiving the other doses had systemic levels above 1 ng/mL on Day 28.

Plasma levels of naltrexone on Day 28 following single dose (3.8 ± 2 ng/mL) and multiple dose (3.9 ± 2) administration of 380 mg Vivitrol in healthy subjects (study # ALK21-005), were above 1 ng/mL in all subjects (n=12).

3. Intrinsic and Extrinsic Factors Affecting Pharmacokinetics of Vivitrol

As indicated previously, pharmacokinetic profile of Vivitrol appears to depend on release of naltrexone from microspheres of drug product injected intramuscularly. Bodyweight was the only significant factor that might affect systemic exposure (AUC) of naltrexone with Vivitrol use. Patients with higher bodyweight have lower systemic exposure (Area under the plasma concentration time curve or AUC). However, clinical trial data indicates that efficacy of Vivitrol is not significantly affected by patient bodyweight.

Population pharmacokinetic analysis was conducted to determine if demographic variables (such as age, sex, race, polysubstance dependency, and laboratory markers of renal and hepatic function) contributed to differences in PK parameter estimates (clearance, volume of distribution) among individuals. None of the covariate – parameter relationships determined by the population PK analysis indicated the need for dose adjustments.

The hepatic impairment study # ALK21-009 revealed that mild and moderate hepatic impairment did not affect pharmacokinetics of naltrexone following Vivitrol administration. Pharmacokinetics of Vivitrol was not determined in patients with severe hepatic impairment. Previously, Bertolotti et. al. (Journal of Hepatology 27: 505-511) demonstrated that although delayed, extent of naltrexone metabolism to 6β-naltrexol in cirrhotic subjects was comparable to healthy subjects. This observation suggests that

extra-hepatic sites may also play a major role in the clearance of naltrexone to 6β-naltrexol. Aldo-keto reductases, the enzymes responsible for conversion of naltrexone to 6β-naltrexol, are expressed primarily in liver but also in brain, heart, kidney, lung, prostate, skeletal muscle, small intestine, spleen and testis. As such, it is unlikely that the CYP inhibitors or inducers affect the pharmacokinetics of Vivitrol.

Since naltrexone is extensively metabolized via hepatic and extra-hepatic sites, renal impairment is not expected to significantly affect pharmacokinetics of Vivitrol.

Following single dose IM injection of 380 mg Vivitrol, naltrexone C_{max} was about 30 to 40% lower in females compared to males; however, the average peak plasma levels in females are still higher compared to oral naltrexone. In addition, $AUC_{0\text{-}28days}$ (AUC over 28 day period) was similar in female and male subjects receiving Vivitrol. Hence, dosage adjustment is not necessary based on sex of patient.

Efficacy and Safety Background for the Advisory Committee Vivitrol NDA 21-897

1 Executive Summary

Vivitrol (naltrexone for extended-release injectable suspension) is a depot formulation of the opioid receptor antagonist, naltrexone, which is approved for treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment. It is now under review for a supplemental indication to prevent relapse in recently-detoxified opioid-dependent patients.

The Applicant has provided evidence of efficacy in the form of a single adequate and well-controlled study conducted in multiple sites in Russia, with supportive evidence from their clinical pharmacology program and reference to literature and to the Agency's previous findings concerning oral naltrexone. The Division agrees with the Applicant's interpretation of the results of the trial with respect to preventing relapse to opioid use, but notes that while the study design (randomized, placebo-controlled, parallel group study of 6 months' duration) is not novel, some of the analytic approaches and concepts are. Furthermore, the application is supported by a single efficacy trial conducted outside the U.S. The Division advised Alkermes, during the development program for this indication, that at least one adequate and well-controlled study would be needed to support the new claim, but that a single study, if sufficiently compelling, taken together with the pharmacodynamic data, could potentially suffice. We agree with Alkermes that the efficacy study provides convincing evidence that Vivitrol prevents relapse to opioid use in recently-detoxified opioid-dependent patients. We will ask the committee to address whether the available efficacy data from these sources are sufficient to conclude that the drug is effective for the intended use.

Notably, the efficacy study was conducted at various sites in Russia. As described in the International Conference on Harmonisation (ICH) *Guideline on Ethnic Factors in the Acceptability of Foreign Clinical Data E5(R1)*, there are sometimes circumstances which make it difficult to accept data from foreign studies based on concerns about extrapolability. This is not a data integrity or quality concern, but a concern about whether "ethnic factors" might render the Russian results inapplicable to the American population in some way. Although the term "ethnic factors" frequently refers to physical or genomic differences, in this case we are primarily concerned with the cultural and societal differences, the differences in the medical care system and the available treatment alternatives, or other differences between the studied population and the American target population. We will ask the committee to address whether there might be a need for a "bridging study" of some type to provide assurance that the drug would be effective in the American population.

The Applicant's submission included pooled safety data from a total of 277 patients with opioid dependence who were treated with Vivitrol during Phase 3 clinical trials, including 177 patients treated for at least 6 months and 89 patients treated for a year or more. In addition, safety data from 573 patients with alcohol dependence were included in the safety database, much of which was reviewed under the original NDA review.

Although the expanded safety database did not identify major new safety issues compared to the established safety profile in the alcohol-dependent population, we noted that the rate of adverse event reporting was distinctly lower in the Russian study compared to the completed studies in the U.S. that were considered under the original NDA review. We have been advised that cultural norms in Russia may influence the reporting of adverse events. While the safety profile in the U.S. alcohol-dependent population has been established via the studies reviewed for the original approval, we believe there may be some indication-specific safety concerns. For example, the risk of opioid overdose in opioid-dependent subjects attempting to overcome the blockade effect is a risk not seen in the alcohol-dependent population. Furthermore, viral hepatitis and HIV infection are much more prevalent in the opioid-dependent than in the alcohol-dependent population. If either of these conditions predisposes patients to adverse events related to Vivitrol (e.g., hepatic effects or effects on immune response), it would be important that these risks be adequately characterized in opioid-dependent patients. We will ask the committee to address whether these, or any additional indication-specific safety concerns, have been adequately addressed by the existing safety data, and whether additional safety data may be needed in the American population.

2 Introduction and Background

Naltrexone is an antagonist at the μ-opiate receptor. An oral formulation of naltrexone was approved in 1984 for the indication "for the blockade of effects of exogenously-administered opioids." This indication was approved after advisory committee consultation when a program of clinical trials in opiate addiction treatment failed to demonstrate efficacy. The pharmacologic effect was well-established, but, as the label notes, "there are no data that demonstrate an unequivocally beneficial effect of REVIA[1] on rates of recidivism among detoxified, formerly opioid-dependent individuals who self-administer the drug."

The incorporation of naltrexone into the treatment of addiction in clinical practice has been not entirely enthusiastic. A general impression that the efficacy is limited has been bolstered by the publication of several negative studies. However, it is generally accepted that poor compliance plays a role in limiting the effectiveness of oral naltrexone in addiction treatment. Therefore, the development of passive-compliance formulations (implants, transdermals, depot injections) was a logical extension of the development of naltrexone.

Vivitrol, a depot formulation of naltrexone, was approved in 2006 for the treatment of alcohol dependence. The original application contained, in addition to efficacy and safety data in the alcohol-dependent population, some safety data in opioid-dependent and dually-dependent patients, as well as a clinical pharmacology study demonstrating the blockade of exogenously administered opioids for >28 days. Shortly after approval of the application, Alkermes embarked on a program to support a supplemental application for the use of Vivitrol in the treatment of opioid dependence.

[1] Note that the original proprietary name was Trexan; the name was changed to ReVia at the time of the approval of an efficacy supplement in 1984 adding an indication "in the treatment of alcohol dependence," noting that "ReVia has not been shown to provide any therapeutic benefit except as part of an appropriate plan of management for the addictions."

2.1 FDA-Approved Products for the Treatment of Opioid Dependence

Other approved products for the treatment of opioid dependence include methadone, levomethadyl acetate (LAAM, no longer marketed), and buprenorphine, all of which are agonist treatments. Treatment of addiction with methadone is limited to closely-regulated Opioid Treatment Programs (OTP), which may limit access to treatment. Buprenorphine treatment may be prescribed by specially-qualified physicians in office practice settings.

The other approved products were supported by a variety of studies with treatment as long as 40 weeks, and various analytic approaches were applied in evaluating the results.

2.2 Applicant's Rationale for Product Development

There is a public health need for a product which is not a controlled substance, does not carry risks of respiratory or CNS depression, does not require the patient to obtain treatment at an OTP, and is not subject to abuse or diversion. The Division agreed with Alkermes that Vivitrol had the potential to meet an important public health need. This application has been accorded Priority Review status in recognition of this potential.

2.3 Opioid Dependence Clinical Development

Alkermes conducted the development program for this indication with advice from the Agency on the trial design and analytic approach.

Alkermes was advised to study patients over a period of time that would allow patients who made substantial improvements in their drug-use behavior (abstinence or near-abstinence) to accrue some degree of physical or psychosocial benefit. There was no evidence to support the idea that very brief periods of abstinence would translate into clinical benefit; therefore, six months was chosen as a reasonable observation period.

The Division also did not believe that analyses focused on group means (such as mean percent of weeks abstinent) would be meaningful, because they did not reflect the experience of individual patients, who might range from complete responders to complete non-responders. Conventional wisdom has held that few, or no, patients could sustain complete abstinence over a significant period of time. However, rather than agreeing a priori that complete abstinence would be an unreasonable expectation, or arbitrarily selecting a drug use pattern short of abstinence that would be considered successful, Alkermes was encouraged to look at the full range of responder definitions, from complete abstinence to no abstinence, but to emphasize the effect of the drug on promoting abstinence or near-abstinence. This analysis was referred to by Alkermes as the "response profile."

Recognizing that patients require some time for engagement in treatment and that patients might also be tempted to "test" the blockade, a "grace period" of one month was allowed during which drug use was not counted in the assessment of response.

3 Review of Efficacy

Evidence of efficacy is provided by a single placebo-controlled study, ALK21-013, together with supportive evidence from a clinical pharmacology study showing that Vivitrol blocks the effects of exogenous opioids. Alkermes also cited published literature and previous Agency findings for ReVia. The approved labeling for ReVia (then Trexan) specifically noted that the product had not been shown to have a beneficial effect "on rates of recidivism among detoxified, formerly opioid-dependent individuals."

3.1 Study Design and Endpoints

Study ALK21-013 was a randomized, parallel and multi-center Phase 3 study conducted in two parts, Part A and Part B. Part A was a double-blind, placebo-controlled assessment of efficacy and safety of 24-week monthly treatment with Vivitrol compared to placebo. Patients who completed Part A continue to Part B, which is an on-going, open-label extension to assess longer term safety and durability of the treatment effect. The evaluation of efficacy is based on the data from Part A.

Eligible patients included those with a current diagnosis of opioid dependence who were actively seeking treatment and who were receiving or had recently received inpatient (up to 30 days) treatment for opioid detoxification. The first dose of study drug was administered on the day of or within one week after discharge from an inpatient treatment facility for opioid detoxification. Each patient was required to be opioid-free (including buprenorphine and methadone) for at least 7 days prior to Dose 1. Throughout the study, opioid use was monitored at each visit through urine drug tests and patients' self-reported opioid use, collected via the Timeline Follow Back (TLFB) method. A naloxone challenge test was performed prior to randomization and repeated at the end of Part A. In addition, a positive urine drug test at any visit during the study prompted an additional naloxone challenge for the respective patient. Patients with a positive naloxone test were discontinued from the study.

A total of 250 eligible opioid-dependent patients were randomized in a ratio of 1:1 to receive Vivitrol 380 mg or placebo. Study treatment was administered as an intramuscular injection every 4 weeks for a total of 6 injections. Randomization was performed using an interactive voice response system (IVRS) and was stratified by gender and site. The trial was conducted at 13 sites in Russia.

As discussed above, because of lack of consensus on what pattern of drug use short of abstinence should be deemed a successful outcome, but recognizing concern that patients might have occasional lapses, the protocol called for analysis of the full range of responses, termed the response profile. In addition, to allow for time for patients to engage in treatment, and to acknowledge that some might test the blockade early in treatment, a grace period of four weeks was allowed during which opioid use, if it occurred, was not considered in the analysis.

The primary efficacy outcome was the response profile based on each patient's rate of opioid-free weeks during the last 20 weeks of the 24-week double-blind treatment period. The rate of opioid-free weeks for each patient was calculated as a percent of the 20 weeks of observation. If the patient provided an opioid-positive urine test, or provided self-report of opioid use, or did not provide a urine test (e.g. due to failure to attend the visit), the week was adjudicated as an opioid-use week. The response profile was generated for each treatment by calculating the cumulative percentage of patients achieving each observed value of the rate of opioid-free weeks. The endpoint is expressed somewhat differently by the Applicant, but the process and meaning are the same.

3.2 Population

A total of 250 patients were randomized to treatment with Vivitrol (N = 126) or placebo (N = 124). Selected demographic and baseline characteristics of the patients are shown in the table below. Patients were primarily male and all but two were white. The groups differed somewhat in terms of the distribution of duration of opiate dependence, with more patients in the Vivitrol group reporting shorter duration.

Characteristics of Patients in Study ALK21-013

Variable/Category	Vivitrol, n=126	Placebo, n=124
Age (years)		
Mean (SD)	29.4 (4.8)	29.7 (3.6)
Range	21 – 52	21 – 43
Sex – n (%)		
Male	113 (89.7%)	107 (86.3%)
Female	13 (10.3%)	17 (13.7%)
Race – n (%)		
White	124 (98.4%)	124 (100%)
Asian	2 (1.6%)	0 (0.0%)
Duration of Opioid Dependence (years)		
Mean	9.1	10.0
SD	4.5	3.9
Range	1 – 26	1 – 21
Distribution of Duration of Opiate Dependence – n (%)		
<5 years	23 (18%)	15 (12%)
5-9 years	36 (29%)	30 (24%)
10-14 years	59 (47%)	65 (52%)
>15 years	8 (6%)	14 (11%)
Distribution of Duration of Most Recent Inpatient Treatment (days) - n(%)		
5-14 days	47 (37%)	40 (32%)
>14 days	79 (63%)	84 (68%)
Opiate used in 30 days prior to baseline assessment		
Heroin	111 (88%)	110 (89%)
Methadone	11 (9%)	18 (15%)
Other opiates/analgesics	21 (17%)	12 (10%)

Patient disposition is illustrated below. Overall, 51% of the Vivitrol-treated patients and 65% of the placebo-treated patients did not complete the full 24 weeks of treatment. The most common reason for discontinuation for both treatment arms was lack of efficacy, cited in 18% of patients in the Vivitrol arm and 27% of patients in the placebo arm. In addition, 14% of placebo-treated patients discontinued due to positive naloxone challenge, which is an indicator of relapse to opioid dependence and therefore of lack of efficacy, for a total of 41% of patients randomized to placebo failing to complete the 24 weeks of treatment due to lack of efficacy. Positive naloxone challenge was cited as a reason for discontinuation in only one Vivitrol-treated patient. Adverse event was cited as a reason for discontinuation in only two patients, both on placebo.

Disposition of Patients in Study ALK21-013

Reason for Discontinuation during Part A (N,%)	**VIVITROL N = 126**	**Placebo N = 124**
Lack of efficacy	22 (18%)	34 (27%)
Subject withdrew consent	18 (14%)	12 (10%)
Positive naloxone challenge	1 (1%)	17 (14%)
Lost to follow-up	6 (5%)	6 (5%)
Investigator judgment	8 (6%)	4 (3%)
Major protocol violation	1 (1%)	2 (2%)
Adverse event	0	2 (2%)
Incarceration	2 (2%)	0
Subject relocated	1 (1%)	0
Treatment goal met	0	0
Lost Motivation	0	0
On-going at the database lock for Part A analysis	62 (49%)	44 (36%)

3.3 Statistical Methodologies

The primary analysis was based on the intent-to-treat population (ITT), which included all randomized patients. For calculation of the rate of opioid-free weeks among the last 20 scheduled visits, all missing urine drug test results including dropouts were imputed as positive for opioid use. The response profiles of the two treatment groups were compared using a two-sided Van der Waerden test. As an additional analysis, the proportion of patients achieving complete abstinence from opioid use in the last 20 weeks in each treatment group was compared using a Chi-square test. Although the response profile was accepted as the primary measure of efficacy during development, the importance and clinical relevance of the latter outcome was emphasized by the Agency.

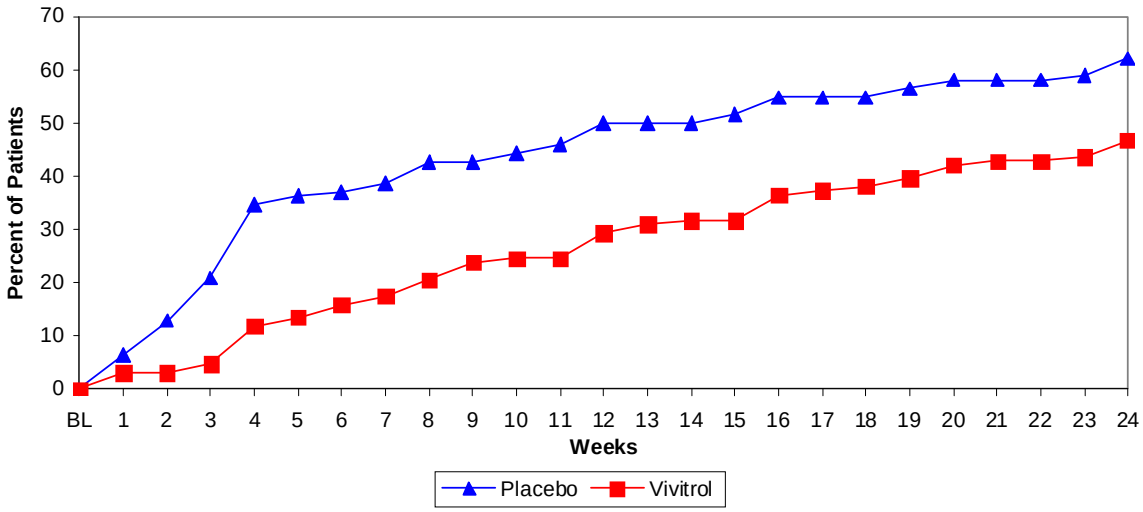
The Applicant explored the influence of stratification factors and other clinically relevant baseline characteristics by analyzing the rate of opioid-free weeks with an analysis of covariance (ANCOVA) model. The ANCOVA model included treatment and sex as

factors. Age, duration of opioid dependence, and duration of last pre-study inpatient detoxification treatment period were included as continuous covariates in the model.

3.4 Results and Conclusions

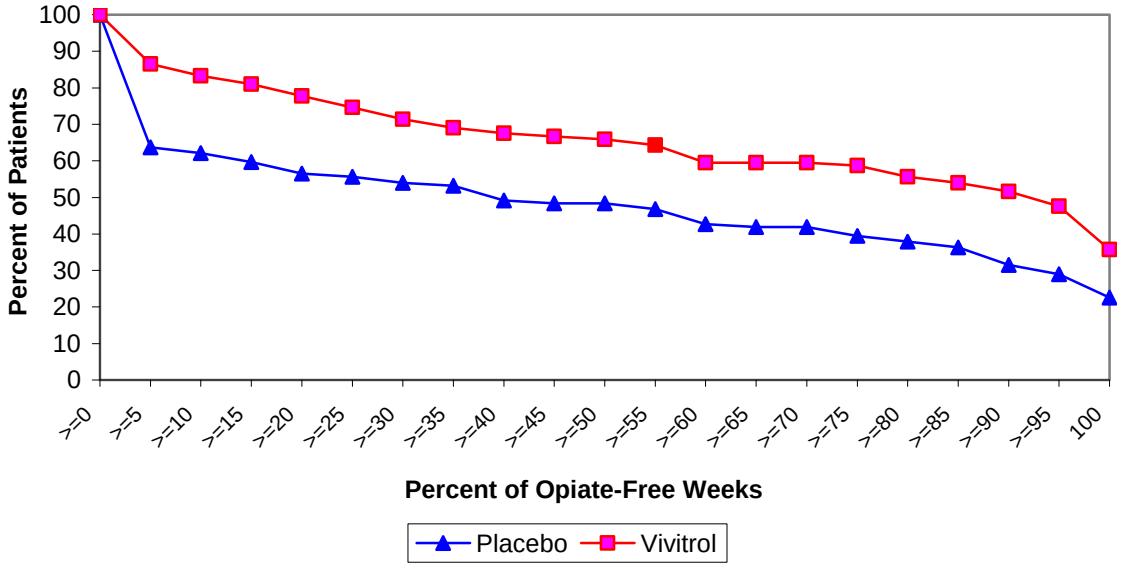
Figure 1 displays the percent of patients who dropped out before each weekly visit from baseline to Week 24 for each treatment. Patients in the placebo group dropped out much faster than the Vivitrol group during the first four weeks before receiving the second dose. Approximately 36% of the patients in the placebo group and 13% of the patients in the Vivitrol group dropped out before Week 5. The dropout pattern was similar between the two groups after Week 4. The primary analysis was based on the data from Week 5 to Week 24. For patients who dropped out before Week 5, all the urine tests in the last 20 weeks were considered as positive.

Figure 1: Percent of Dropouts by Weekly Visit



The results of the primary analysis are shown in Figure 2. The horizontal axis denotes the percent of opioid-free weeks out of 20, and the vertical axis denotes the percent of patients achieving the various rates of opioid-free weeks. For example, approximately 64% of the patients in the placebo group had at least 5% opioid-free weeks, which corresponds to at least one opioid-free week among the last 20 visits. In comparison, approximately 87% of the patients in the Vivitrol group had at least one opioid-free week. The difference between these numbers reflects the difference of the percent of patients who dropped out before Week 5 between the treatment groups. The response profiles were significantly different between the two groups as compared by the Van der Waerden test (p-value=0.0002).

Figure 2: Response Profile Based on Percent of Opioid-Free Weeks



As can be seen in Figure 2 and shown in tabular form below, 23% of patients in the placebo group and 36% of patients in the Vivitrol group achieved complete abstinence from Week 5 to Week 24. The difference was significant as evaluated using a Chi-square test (p-value=0.0224).

Total Abstinence from Opioid during the Last 20 Weeks

Analysis Population	Percent of Patients Opioid-Free for all 20 Weeks		Chi-Square test P-value
	Placebo	Vivitrol	
ITT	28/124 (23%)	45/126 (36%)	0.0224

Because more patients in the Vivitrol group reported a shorter duration of opioid dependence at baseline compared to patients in the placebo group, subgroup analyses were conducted to explore the potential impact of this variable. In this analysis, groups were defined as having years of duration less than five years, between five to nine years, ten to 15 years and 16 years or more. The analyses yielded a consistent treatment effect across groups.

Exploratory analyses of the influence of baseline characteristics including age, sex, and duration of opioid dependence on the rate of opioid-free weeks also did not reveal any significant effects for the baseline variables. An exploratory analysis of pre-study detoxification was also conducted. In the Applicant's analysis, duration of pre-study detoxification was grouped based on tertiles (i.e. 5–14 days, 15–19 days, 20–67 days).

This analysis resulted in a better response profile for the placebo group compared to the Vivitrol group for patients with duration of detoxification in the range from 15 to 19 days. There was no explanation identified for this finding. A further subgroup analysis that classified duration of pre-study detoxification as within two weeks and more than two weeks revealed a consistent treatment effect.

3.5 Additional Supportive Data

Additional support for the efficacy of Vivitrol derives from StudyALK21-004, a Phase 2, double-blind, parallel-group assessing the degree and duration of opiate blockade conferred by the Vivitrol formulation at various doses. This study is reviewed by Srikanth Nallani, Ph.D., in a separate document.

3.6 Discussion

The evidence of efficacy provided includes a single placebo-controlled efficacy study taken together with pharmacodynamic data showing that Vivitrol blocks the effects of exogenously administered opioids for the entire inter-dose period. The Division advised Alkermes, during the development program for this indication, that at least one adequate and well-controlled study would be needed to support the new claim, but that a single study, if sufficiently compelling, taken together with the pharmacodynamic data, could potentially suffice. We agree with Alkermes that the efficacy study provides convincing evidence that Vivitrol prevents relapse to opioid use in recently-detoxified opioid-dependent patients. We will ask the committee to address whether the available efficacy data from these sources are sufficient to conclude that the drug is effective for the intended use.

Notably, the efficacy study was conducted at various sites in Russia. As described in the International Conference on Harmonisation (ICH) *Guideline on Ethnic Factors in the Acceptability of Foreign Clinical Data E5(R1)*, there are sometimes circumstances which make it difficult to accept data from foreign studies based on concerns about extrapolability. This is not a data integrity or quality concern, but a concern about whether "ethnic factors" might render the Russian results inapplicable to the American population in some way. Although the term "ethnic factors" frequently refers to physical or genomic differences, in this case we are primarily concerned with the cultural and societal differences, the differences in the medical care system and the available treatment alternatives, or other differences between the studied population and the American target population. We will ask the committee to address whether there might be a need for a "bridging study" of some type to provide assurance that the drug would be effective in the American population.

The table below illustrates some of the demographic features of the clinical trial populations (alcohol-dependent patients studied in U.S. studies, opioid-dependent patients studied in U.S. Study ALK21-006) as well as some data from the National Survey on Drug Use and Health (NSDUH) pertinent to the demographics of the opioid-dependent population in the U.S.

Demographic & Baseline Characteristics	Alcohol Dependent	Opioid-Dependent		NSDUH/ SAMSHA Data
Variable/Category		**US**	**Russia**	
Subjects Dosed	759	121	250	
Age (yrs)				
N	759	121	250	
Median	44	31.0	30	
Mean	**44.1**	**34.1**	**29.6**	
SD	10.4	10.8	4.2	
Min - Max	19-79	18-61	21-52	
Gender, N(%)				
Male	**498 (65.6)**	**80 (66.1)**	**220 (88.0%)**	69%
Race/Ethnicity, N(%)				
White	**639 (84.2)**	**99 (81.8)**	**248 (99.2%)**	91%
Black	57 (7.5)	12 (9.9)	0	
Hispanic	35 (4.6)	7 (5.87)	0	
Asian	**3 (0.4)**	**2 (1.7)**	**2 (0.8%)**	
Native American	4 (0.5)	1 (0.8)	0	
Other	17 (2.2)	0	0	
BMI (kg/m2)				
Mean	**27.1**	**26.3**	**23.2**	
Type of Opioid Dependence (N, %)				
Heroin		**26 (42.6%)**	**221 (88.4%)**	300K US
Methadone			**29 (11.6%)**	
Other Opioids/Analgesics		**33 (54.1%)**	**33 (13.2%)**	1.7 mil US
Hepatitis C		**10 (8%)**	**222 (88.8%)**	

4 Review of Safety

The Applicant's submission included pooled safety data from a total of 277 patients with opioid dependence who were treated with Vivitrol during Phase 3 clinical trials, including 177 patients treated for at least 6 months and 89 patients treated for a year. The data derive from two studies: the single placebo[2]-controlled study, ALK21-013, and an open-label safety study conducted as part of the original NDA, ALK21-006 (and its extension, ALK21-006-EXT). This study enrolled patients with alcohol dependence, opioid dependence, and mixed dependence in order to provide some safety data in the opioid-dependent population prior to approval for the alcohol dependence indication, to address risks in off-label use.

In addition, safety data from 573 patients with alcohol dependence, who were treated with Vivitrol, were included in the safety database, much of which was reviewed under the original NDA review. The table below illustrates overall extent of exposure in clinical trials in patients. Additional exposures in volunteers in clinical pharmacology studies are not reflected in the table below.

Extent of Exposure to Vivitrol in Clinical Trial Database

	≥1 Dose	**≥6 Doses**	**≥12 Doses**	**≥24 Doses**	**≥36 Doses**
Opioid-dependent patients					
Russian	173	108	49		
American	104	69	40	7	
Total opioid-dependent	277	177	89	7	
Non-opioid-dependent (alcohol-dependent)	573	339	199	85	44
Total patients	850	516	288	92	44

[2] The placebo in all placebo-controlled studies consisted of microspheres and vehicle without naltrexone.

The demographic characteristics of the opioid-dependent patients are illustrated in the table below.

Demographic Characteristics of the Opioid-Dependent Safety Population

			Vivitrol				
		Placebo ALK21-013	**ALK21-013**	**ALK21-006**	**ALK21-006 + 013**	**Oral NTX ALK21-006**	**All patients**
Patients Dosed		124	126	101	227	20	371
Age	N	124	126	101	227	20	371
	Median	30.0	29.0	34.0	30.0	29.0	30.0
	Mean	29.7	29.4	34.9	31.8	30.2	31.0
	SD	3.6	4.8	11.3	8.7	6.9	7.4
	Min - Max	21 – 43	21 – 52	18 – 61	18 – 61	21 - 42	18 -61
Gender, N (%)	Male	107 (86.3)	113 (89.7)	68 (67.3)	181 (79.7)	12 (60.0)	300 (80.9)
	Female	17 (13.7)	13 (10.3)	33 (32.7)	46 (20.3)	8 (40.0)	71 (19.1)
Race/ Ethnicity	White	124 (100.0)	124 (98.4)	85 (84.2)	209 (92.1)	14 (70.0)	347 (93.5)
	African American/Black	0	0	10 (9.9)	10 (4.4)	2 (10.0)	12 (3.2)
	Hispanic	0	0	5 (5.0)	5 (2.2)	2 (10.0)	7 (1.9)
	Asian	0	2 (1.6)	1 (1.0)	3 (1.3)	0	3 (0.8)
	Native American	0	0	0	0	2 (10.0)	2 (0.5)
Height (cm)	N	124	126	100	226	20	370
	Median	176.0	175.5	173.5	175.0	171.5	175.0
	Mean	176.0	175.5	173.6	174.7	172.3	175.0
	SD	7.3	7.5	9.8	8.6	9.0	8.2
	Min - Max	155 – 198	154 – 194	154 – 196	154 – 196	157 – 186	154 – 198
Weight (kg)	N	124	126	101	227	20	371
	Median	71.0	70.0	79.0	72.0	71.0	71.0
	Mean	72.0	71.7	79.7	75.3	76.3	74.2
	SD	10.9	9.8	19.1	15.2	17.8	14.1
	Min - Max	50 – 121	52 – 105	46 – 134	46 – 134	51 - 118	46 - 134

		ALK21-013 patients		ALK21-006 patients Vivitrol & Oral NTX			All patients
BMI (kg/m^2)	N	250		120			370
	Median	22.9		25.2			23.3
	Mean	23.2		26.3			24.2
	SD	2.7		5.7			4.2
	Min - Max	17 – 33		16 – 48			16 – 48
Preferred Opioid[a]	N	250		61			
	Heroin	211 (88.4%)		26 (42.6%)			
	Methadone	29 (11.6%)					
	Other opioids/analgesics	33 (13.2%)		1 (1.6%)			
	Prescription Opioids			33 (54.1%)			
	Rx opioids & heroin			1 (1.6%)			

[a] Based on data for the 30 days prior to dosing collected using the Addiction Severity Index (ASI) for the ALK21-013 population; Patients in the ALK21-006 were asked about their primary opioid of abuse.

A considerable number of patients with a medical history of hepatitis C (89% of patients) and human immunodeficiency virus (HIV) infection (41% of patients) were included in ALK21-013. In ALK21-006, patients with a history of HIV were excluded. Of the 121 opioid-dependent patients in ALK21-006, 10 (8%) had a medical history of hepatitis C and 1 (0.8%) had a history of "hepatitis" without a more specific designation as to type.

In the alcohol-dependent population, patients were again predominantly male (66%), white (84%) and older than the opioid-dependent population with a mean age of 44.1 years. The mean height, weight, and BMI were 173.8 cm, 82.2 kg, and 27.1kg/m^2, respectively.

Additionally, Alkermes estimates that approximately 42,000 patients have been treated with Vivitrol since initial approval.

4.1 Major Safety Results

4.1.1 Deaths

There were no deaths in opioid-dependent patients in clinical trials of Vivitrol.

In the pre-marketing safety database, there were five deaths, all in Vivitrol-treated alcohol-dependent patients. The causes of deaths were completed suicide (n = 2), as well as homicide, pancreatic cancer, and coronary atherosclerosis (n = 1 each). In Alkermes' post-marketing safety database, there are 19 reports with fatal outcomes, most commonly due to completed suicide, opioid overdose (3), and sequelae of alcohol use or intoxication.

4.1.2 Serious Adverse Events

During the double-blind, placebo-controlled portion of ALK21-013, four (3%) of patients in the placebo arm had a serious adverse event (SAE), compared with three (2%) of patients treated with Vivitrol. The 3 SAEs occurring in Vivitrol-treated patients were of infectious etiology; 2 HIV-infected patients had SAEs of HIV stage 3 and herpes virus infection/AIDS, while the third patient had adnexitis. No patients on placebo had progression to later stages of HIV infection.

In the pooled safety database of opioid-dependent patients, including data from ALK21-013 and open-label study ALK21-006 and its extension, overall there were 33 patients experiencing SAEs during Vivitrol treatment up to a year or longer. In the first six months of study participation, 16 of 277 patients (7%) experienced at least one SAE. Most events occurred in only a single patient; several events involved either sequelae of addiction (e.g., accidental injuries) or hospitalization for addiction treatment. Other SAEs occurring in more than one of the Vivitrol-treated patients included ten events involving depression, suicidal ideation, behavior and attempts, as well as two apparent accidental overdoses.

4.1.3 Adverse Events Leading to Discontinuation

No Vivitrol-treated patients in the efficacy study, ALK21-013, discontinued due to adverse events (vs. 2 (2%) on placebo). However, among opioid-dependent patients who participated in the open-label safety study, ALK21-006 and its extension, 11 patients (11%) discontinued due to adverse events in the first 6 months of participation (vs. 0 on oral naltrexone), with an additional 6 discontinuing due to AEs later in the study. Some events leading to discontinuation were coded as AEs but represented hospitalizations for treatment of addiction (i.e., lack of efficacy) and 4 cases were discontinuations due to pregnancy.

The only other AEs associated with discontinuation in more than a single individual were terms related to suicide attempt/behavior (in three Vivitrol-treated patients); an additional case coded as "delirium" appears to have occurred in the context of a possible suicidal ingestion of medications in a fourth Vivitrol-treated patient.

4.1.4 Common Adverse Events

The adverse event profile of Vivitrol in U.S. patients, primarily with alcohol dependence, but also including some patients with opioid dependence or mixed dependence, was characterized in the safety database reviewed in the original NDA submission. The adverse event table from the approved labeling is shown in Appendix A.

Note that this table includes those events which occurred in at least 5% of patients using the MedDRA High Level Group Term. The MedDRA coding system includes many specific Preferred Terms (approximately ten times the number used in the COSTART coding system) that are systematically grouped together into Higher Level Terms and then into Higher Level Group Terms (HLGT). Because many different Preferred Terms had been used to capture similar events of interest (e.g., injection site pain, injection site tenderness), the data was analyzed with attention to the grouped terms to identify events of interest. Using this approach, gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea, anorexia) were very common and clearly drug-related (approximately 33% of Vivitrol-treated patients vs. 11% of placebo-treated). Injection site reactions were reported in 65% of Vivitrol-treated patients, with specific types of reactions (induration, pain, nodules, swelling) appearing to be clearly drug-related.

In the expanded database supporting this application, AE data in the opioid-dependent population derived from two studies: the placebo-controlled study conducted in Russia (ALK21-013), and the open-label safety study conducted in the US prior to the original NDA approval (ALK21-006). Upon review of the data, it became apparent that the rate of adverse event reporting was very different between the two studies, perhaps reflecting cultural differences in the populations with regard to willingness to report adverse events. Therefore, pooling of the Vivitrol-treated groups and subsequent comparison to the placebo group, which included only participants in the Russian study, did not seem appropriate. Therefore, the AEs occurring in at least 5% (at the Higher Level Group Term level) of any group are shown in the table in Appendix B, broken out by study. This

tabulation permits comparison of the placebo arm vs. the Vivitrol arm in the ALK21-013 study, and a comparison of the AE experience of the Vivitrol-treated opioid-dependent patients in US study ALK21-006 with the Vivitrol-treated opioid-dependent patients in Russian study ALK21-013. In addition, the table includes the Vivitrol 380 mg arm and the placebo arm from the US study ALK21-003 in alcohol-dependent patients.

Only six High Level Group Terms (which subsume multiple preferred terms) were reported in at least 5% of patients in either arm. In the table below, generated from Alkermes' submitted datasets, HLGTs in which at least 5% of patients in either arm reported an AE during the placebo-controlled portion of ALK21-013 are shown. In this analysis, each patient is counted once for a particular HLGT, even if he or she experienced more than one event in that grouping. For example, patients listed under "hepatobiliary investigations" had one or more abnormal laboratory findings that were reported as adverse events; many had several. As this table illustrates, the patients in ALK21-013 reported very few adverse events.

Common Adverse Events in Study ALK21-013

	Placebo N= 124		Vivitrol N=126	
HLGT	N	%	N	%
Hepatobiliary investigations	10	8%	24	19%
Infections - pathogen unspecified	9	7%	14	11%
Viral infectious disorders	6	5%	9	7%
Sleep disorders and disturbances	1	1%	8	6%
Administration site reactions	2	2%	7	6%
Vascular hypertensive disorders	4	3%	6	5%

In contrast, opioid-dependent patients participating in the US trial ALK21-006 had an adverse event profile that was more similar to the established safety profile. At least 5% of patients reported adverse events coding to one of the following HLGTs:

Common Adverse Events in Opioid-Dependent Patients in Study ALK21-006

HLGT	N	%
Infections - pathogen unspecified	33	33%
Gastrointestinal signs and symptoms *(primarily nausea, abdominal pain)*	23	23%
Headaches	17	17%
General system disorders NEC *(primarily fatigue)*	14	14%
Sleep disorders and disturbances	14	14%
Musculoskeletal and connective tissue disorders NEC *(includes various types of pain)*	12	12%
Neurological disorders NEC *(sedation/lethargy; ataxia/dizziness)*	11	11%
Muscle disorders *(myalgia/muscle spasms)*	10	10%
Gastrointestinal motility and defaecation conditions *(diarrhea)*	9	9%
Depressed mood disorders and disturbances	8	8%
Enzyme investigations NEC *(elevated CPK)*	7	7%
Respiratory disorders NEC *(dyspnea)*	7	7%
Bacterial infectious disorders	6	6%
Viral infectious disorders	6	6%
Physical examination topics *(weight increased/decreased)*	6	6%
Appetite and general nutritional disorders *(anorexia)*	6	6%
Anxiety disorders and symptoms	6	6%
Hepatobiliary investigations	5	5%

In the pre-marketing safety database, most terms related to infection occurred at similar rates in Vivitrol-treated and placebo-treated groups and were therefore not included in the AE table in labeling. This is a notable difference between the established safety profile and the safety experience in the expanded database. Based on the results of the placebo-controlled portion of ALK21-013, it appears that events coded to the "Infections and Infestations" System Organ Class (SOC) are more common in Vivitrol-treated than placebo-treated patients.

Moreover, AEs in the "Hepatobiliary Investigations" HLGT were more common in Vivitrol-treated than in placebo-treated patients in this study. Correction for different durations of exposure, using person-time calculations, does not account for this finding.

Both of these may represent Vivitrol-related events not previously identified in the alcohol-dependent population.

4.1.5 AEs of Special Interest

Based on mechanism of action, and on safety concerns identified during the original NDA review and in postmarketing safety experience, the following safety issues were given special attention:

1. Serious injection site reactions
2. Eosinophilic Pneumonia
3. Allergic Reactions
4. Hepatic effects
5. Depression/Suicidality
6. Accidental opioid overdose
7. Precipitation of opioid withdrawal

4.1.5.1 Serious Injection Site Reactions

In the pre-marketing clinical trials, a case of a very severe injection site reaction requiring surgery was reported and included in labeling. During the initial approximately 18 months of marketing, a number of additional cases were reported to Alkermes through their postmarketing pharmacovigilance program, and a supplement was submitted to add additional warnings to the label. On review, it appeared that the events might be attributable to accidental subcutaneous, rather than intramuscular injection. Therefore, in addition to changes to labeling, a REMS providing a MedGuide to patients alerting them to be vigilant about injection site reactions, and safety communications to alert providers to the risk, a new kit was developed which will provide a 2" administration needle in addition to the currently-provided 1.5" needle.

No new serious injection site reactions were reported in the expanded safety database supporting this supplement. Alkermes' postmarketing pharmacovigilance indicates that the number of serious ISRs, and, in particular, the number requiring surgery, has declined since the initial group of reports which prompted the implementation of the REMS.

Alkermes made the 2" needle (soon to be included in the commercially-marketed kit) available as an option to the investigators in Study ALK21-013. However, it was employed only for 9 patients. The ALK21-013 population was generally leaner than the participants in the US trials and therefore may be less vulnerable to accidental subcutaneous injection.

4.1.5.2 Eosinophilic Pneumonia

Two cases of eosinophilic pneumonia were reported in the pre-marketing safety database and the risk of eosinophilic pneumonia is included in the approved labeling as a warning. No new cases of eosinophilic pneumonia were reported in the expanded clinical trial safety database supporting this supplement. Two cases are included in Alkermes' postmarketing pharmacovigilance database.

4.1.5.3 Allergic Reactions

Because of the seriousness of the injection site reaction and eosinophilic pneumonia cases observed in the pre-marketing safety database, and the observation that Vivitrol treatment was also associated with increases in eosinophil count, a general concern about allergic reactions to Vivitrol existed. Therefore, Alkermes was asked to analyze the expanded safety database using the Standardized MedDRA Query (SMQ) approach which aggregates all possible terms from various System Organ Classes to identify potential events of interest.

Identified events were reviewed individually. There were no specific listings of anaphylaxis, however, there were events coded to terms angioedema, face edema, urticaria, hypersensitivity and drug hypersensitivity. In general, the events identified by the SMQ search were assessed as mild or moderate. While not seen as preferred terms in these analyses and, in general, not a common event, cases of anaphylaxis have been identified in postmarketing experience and this potential will be added to labeling.

4.1.5.4 Hepatic Effects

Naltrexone's hepatic effects are noted in the labeling for both oral naltrexone and Vivitrol. Although there was an initial belief that Vivitrol might be less prone to cause hepatic effects than oral naltrexone, the data have not borne this out. However, no serious hepatic events related to Vivitrol were noted pre-marketing.

Although the original safety database for Vivitrol included patients with some degree of alcohol-related liver injury, few patients with viral hepatitis were previously studied. In Study ALK21-013, 89% of patients had serologic evidence of Hepatitis C. Therefore, the expanded safety database provides information on the effects of Vivitrol in patients with viral hepatitis, which is highly prevalent in the new target population.

In the opioid-dependent population, there was no pattern of adverse events involving the liver suggesting a role of Vivitrol other than AEs in the "Investigations" SOC. These represent hepatic laboratory abnormalities that were reported as AEs based on investigator judgment. These events were more common in the Vivitrol-treated than placebo-treated patients in Study ALK21-013. It was noted by Alkermes that Hepatitis C is associated with fluctuations in hepatic enzymes, and that the observed abnormalities might be unrelated to study drug. To explore the possibility that a higher rate of study completion in the Vivitrol arm compared to the placebo arm simply gave more opportunity to observe these fluctuations in the Vivitrol arm, a person-time analysis was conducted and revealed that, even corrected for exposure time, AEs of hepatic enzyme abnormality were more common in the Vivitrol-treated than in the placebo-treated patients, consistent with the labeled hepatic effects of Vivitrol.

No Hy's Law cases have been identified and few extreme elevations were observed.

4.1.5.5 Depression/Suicidality

Because of the potential for blockade of opiate receptors to interfere with endogenous opioids, the mechanism of action of naltrexone raises concern about dysphoria and depression. In the pre-marketing safety database, it was observed that adverse events of a suicidal nature (suicidal ideation, suicide attempts, completed suicides) were infrequent overall, but were more common in patients treated with Vivitrol than in patients treated with placebo (1% vs. 0). Two completed suicides occurred, both involving patients treated with Vivitrol. Adverse events involving depressed mood were reported by 10% of patients treated with Vivitrol as compared to 5% of patients treated with placebo injections in the 24-week, placebo-controlled pivotal trial in alcohol dependence.

Using the SMQ for Depression and Suicide/Self-Injury, Alkermes identified patients who experienced events coded to terms of interest. In the first six months of study participation, there were 2 patients (2%) on placebo and 1 patient (1%) of patients on Vivitrol in the placebo-controlled trial ALK21-013 who had at least 1 AE identified by the depression and suicide/self-injury SMQ. In the open-label trial, ALK21-006, during the first six months of treatment some patients were randomized to Vivitrol and some were randomized to oral naltrexone. Of the 101 patients treated with Vivitrol, 18 (18%) compared with 3 patients on oral naltrexone (15%) had at least 1 AE identified by the depression and suicide/self-injury SMQ.

In the time period representing > 24 weeks of participation, no patients in the placebo-controlled trial were identified as experiencing an adverse event of interest. In the open-label trial, 20% of those continuing on Vivitrol in this period (12 patients) and 23% on oral naltrexone (n=3) had 1 AE identified by this SMQ. For those continuing on Vivitrol, 6 patients (10%) had depression or depressed mood, while 1 AE of depression was identified by the SMQ for patients on oral naltrexone in this period (8%).

Review of the SAEs for the opioid-dependent population, as noted above, identified 10 cases of depression/suicidality among the narratives. Nine of these cases were either coded to terms involving suicidal ideation or behavior or provided information in the narratives suggesting suicidality.

4.1.5.6 Accidental Opioid Overdose

Accidental opioid overdose is a risk for patients who attempt to overcome the blockade using large quantities of opioids, and for patients who use opioids after missing a dose of Vivitrol or dropping out of treatment. These patients often have reduced tolerance compared to pre-treatment levels and may misjudge the dose of opioid to use. This is an indication-specific safety concern that is not expected to apply to patients using the product for the currently-approved application, but is likely to occur more frequently if the product is marketed for the new indication.

No cases of accidental opioid overdose were observed in Study ALK21-013. There were four cases of opioid overdose, two requiring hospitalization, among the 101 opioid-dependent participants in Study ALK21-006. None were fatal.

Some off-label use of Vivitrol, or use in patients with both alcohol and opioid dependence, has occurred during the marketing of the product, although the extent is difficult to quantify. Review of the Applicant's post-marketing experience summary and of the AERS database revealed three cases, two fatal, in which patients overdosed on opiates approximately a month following their last Vivitrol injection (i.e., at the time blockade was waning). Another fatal overdose occurred approximately 3 months after the patient was lost to follow-up.

The labeling currently carries language describing the potential for accidental opioid overdose.

4.1.5.7 Precipitation of Opioid Withdrawal

Patients who are physically-dependent on opioids at the time of dosing with Vivitrol are likely to experience precipitated opioid withdrawal. Prior to initial dosing, participants in Study ALK21-013 were required to undergo a Narcan challenge test, in which a small dose of naloxone was administered to establish that the patient was not currently opioid-dependent. Thereafter, patients whose urine toxicology results indicated opioid use were re-challenged with naloxone prior to further Vivitrol dosing; patients with a positive response (evidence of opioid withdrawal) were discontinued from Vivitrol treatment.

No patients in Study ALK21-013 experienced adverse events that were coded to the term "withdrawal" or related terms. Two patients in Study ALK21-006 experienced events coded as "withdrawal syndrome." Common withdrawal-related symptoms such as diarrhea and abdominal pain were reported with some frequency, but these were identified as drug-related events in the alcohol-dependent population as well.

Alkermes provided data on the experience with opioid withdrawal in the postmarketing setting. There were 32 cases of opioid withdrawal reported.

The current labeling includes a Warning about precipitation of withdrawal and the need to consider using a naloxone challenge test if current physical dependence on opioids is suspected.

4.2 Safety Summary

The overall safety profile in opioid-dependent patients is similar to the established safety profile in the Vivitrol label with the following indication-specific observations:

- Opioid overdose, observed in the opioid-dependent population, did not occur in alcohol-dependent patients. Although these events are not common, both the clinical trial data and the post-marketing safety experience confirm that accidental overdose may occur in opioid-dependent patients treated with Vivitrol, particularly at the end of the dosing interval.
- It is possible that the opioid-dependent population may be more vulnerable to the hepatic effects of naltrexone, particularly patients with viral hepatitis.
- Vivitrol-treated opioid-dependent patients reported more infections of all types (viral, fungal, bacterial) than patients treated with placebo.

4.3 Discussion

Although the expanded safety database did not identify major new safety issues compared to the established safety profile in the alcohol-dependent population, we noted that the rate of adverse event reporting was distinctly lower in the Russian study compared to the completed studies in the U.S. that were considered under the original NDA review. We have been advised that cultural norms in Russia may influence the reporting of adverse events. While the safety profile in the U.S. alcohol-dependent population has been established via the studies reviewed for the original approval, we believe there may be some indication-specific safety concerns. For example, the risk of opioid overdose in opioid-dependent subjects attempting to overcome the blockade effect is a risk not seen in the alcohol-dependent population. Furthermore, viral hepatis and HIV infection are much more prevalent in the opioid-dependent than in the alcohol-dependent population. If either of these conditions predisposes patients to adverse events related to Vivitrol (e.g., hepatic effects or effects on immune response), it would be important that these risks be adequately characterized in opioid-dependent patients. We will ask the committee to address whether these, or any additional indication-specific safety concerns, have been adequately addressed by the existing safety data, and whether additional safety data may be needed in the American population.

5 Conclusion

We agree with Alkermes that the efficacy study provides convincing evidence that Vivitrol prevents relapse to opioid use in recently-detoxified opioid-dependent patients. However, the data derive from a single study, conducted in a population with some demographic, cultural, and societal differences from the target population. We will ask the committee to address whether the available efficacy data are sufficient to conclude that the drug is effective for the intended use.

Although the expanded safety database did not identify major new safety issues compared to the established safety profile in the alcohol-dependent population, we noted that the rate of adverse event reporting was distinctly lower in the Russian study compared to the completed studies in the U.S. that were considered under the original NDA review, perhaps due to cultural factors. We will ask the committee to address whether indication-specific safety concerns have been adequately addressed by the existing safety data, or if additional safety data may be needed in the American population.

Appendix A: Adverse Events from Approved Labeling

Treatment-emergent Adverse Reactions (Reactions in ≥ 5% of patients with alcohol dependence treated with VIVITROL and occurring more frequently in the combined VIVITROL group than in the placebo group)

Body System	Adverse Reaction / Preferred Term	Placebo		Naltrexone for extended-release injectable suspension							
		N=214		400 mg N=25		380 mg N=205		190 mg N=210		All N=440	
		N	%	N	%	N	%	N	%	N	%
Gastrointestinal Disorders	Nausea	24	11	8	32	68	33	53	25	129	29
	Vomiting NOS	12	6	3	12	28	14	22	10	53	12
	Diarrhea[a)]	21	10	3	12	27	13	27	13	57	13
	Abdominal pain[b)]	17	8	4	16	23	11	23	11	50	11
	Dry Mouth	9	4	6	24	10	5	8	4	24	5
Infections & Infestations	Pharyngitis[c)]	23	11	0	0	22	11	35	17	57	13
Psychiatric Disorders	Insomnia, sleep disorder	25	12	2	8	29	14	27	13	58	13
	Anxiety[d)]	17	8	2	8	24	12	16	8	42	10
	Depression	9	4	0	0	17	8	7	3	24	5
General Disorders & Administration Site Conditions	Any ISR	106	50	22	88	142	69	121	58	285	65
	Injection site tenderness	83	39	18	72	92	45	89	42	199	45
	Injection site induration	18	8	7	28	71	35	52	25	130	30
	Injection site pain	16	7	0	0	34	17	22	10	56	13
	Other ISR (primarily nodules, swelling)	8	4	8	32	30	15	16	8	54	12
	Injection site pruritus	0	0	0	0	21	10	13	6	34	8
	Injection site ecchymosis	11	5	0	0	14	7	9	4	23	5
	Asthenic conditions[e)]	26	12	3	12	47	23	40	19	90	20
Musculoskeletal & Connective Tissue Disorders	Arthralgia, arthritis, joint stiffness	11	5	1	4	24	12	12	6	37	9
	Back pain, back stiffness	10	5	1	4	12	6	14	7	27	6

Body System	Adverse Reaction / Preferred Term	Placebo		Naltrexone for extended-release injectable suspension							
		N=214		400 mg N=25		380 mg N=205		190 mg N=210		All N=440	
		N	%	N	%	N	%	N	%	N	%
	Muscle cramps[f)]	3	1	0	0	16	8	5	2	21	5
Skin & Subcutaneous Tissue Disorders	Rash[g)]	8	4	3	12	12	6	10	5	25	6
Nervous System Disorders	Headache[h)]	39	18	9	36	51	25	34	16	94	21
	Dizziness, syncope	9	4	4	16	27	13	27	13	58	13
	Somnolence, sedation	2	1	3	12	8	4	9	4	20	5
Metabolism & Nutrition Disorders	Anorexia, appetite decreased NOS, appetite disorder NOS	6	3	5	20	30	14	13	6	48	11

a) Includes the preferred terms: diarrhea NOS; frequent bowel movements; gastrointestinal upset; loose stools
b) Includes the preferred terms: abdominal pain NOS; abdominal pain upper; stomach discomfort; abdominal pain lower
c) Includes the preferred terms: nasopharyngitis; pharyngitis streptococcal; pharyngitis NOS
d) Includes the preferred terms: anxiety NEC; anxiety aggravated; agitation; obsessive compulsive disorder; panic attack; nervousness; post-traumatic stress
e) Includes the preferred terms: malaise; fatigue (these two comprise the majority of cases); lethargy; sluggishness
f) Includes the preferred terms: muscle cramps; spasms; tightness; twitching; stiffness; rigidity
g) Includes the preferred terms: rash NOS; rash papular; heat rash
h) Includes the preferred terms: headache NOS; sinus headache; migraine; frequent headaches

Appendix B: see attached document

Week 0 through 24

Most Frequently Reported (>=5% in any Group) Adverse Events in Combined ISS

Preferred Term (MedDRA)	Placebo ALK21-013	VIVITROL ALK21-013	VIVITROL ALK21-006 Opiod Only	Placebo ALK21-003	VIVITROL ALK21-003
Subjects dosed	124	126	101	209	205
Subjects with an AE	40 (32)	63 (50)	87 (86)	181 (87)	187 (91)
System Organ Class (MedDRA)					
High Level Group Term (MedDRA)					
High Level Term (MedDRA)					
Preferred Term (MedDRA)					
Subjects dosed	124	126	101	209	205
Subjects with an AE	40 (32)	63 (50)	87 (86)	181 (87)	187 (91)
Gastrointestinal disorders	6 (5)	6 (5)	30 (30)	69 (33)	115 (56)
Diarrhoea (excl infective)	0	0	9 (9)	22 (11)	35 (17)
Diarrhoea	0	0	5 (5)	20 (10)	26 (13)
Gastrointestinal signs and symptoms	0	0	5 (5)	20 (10)	26 (13)
Abdominal pain upper	2 (2)	1 (<1)	23 (23)	50 (24)	88 (43)
Nausea and vomiting symptoms	1 (<1)	0	10 (10)	12 (6)	22 (11)
Nausea	0	0	3 (3)	3 (1)	13 (6)
Vomiting	1 (<1)	0	8 (8)	9 (4)	9 (4)
Salivary gland conditions	2 (2)	1 (<1)	9 (9)	31 (15)	75 (37)
General disorders and administration site conditions	2 (2)	1 (<1)	9 (9)	23 (11)	68 (33)
Gastrointestinal and abdominal pains (excl oral and throat)	1 (<1)	0	1 (<1)	12 (6)	28 (14)
Abdominal pain	0	0	3 (3)	9 (4)	11 (5)
Abdominal pain upper	5 (4)	8 (6)	22 (22)	50 (24)	90 (44)

N (%) of Subjects

Week 0 through 24

Most Frequently Reported (>=5% in any Group) Adverse Events in Combined ISS

System Organ Class (MedDRA) High Level Group Term (MedDRA) High Level Term (MedDRA) Preferred Term (MedDRA)	Placebo ALK21-013	VIVITROL ALK21-013	VIVITROL ALK21-006 Opiod Only	Placebo ALK21-003	VIVITROL ALK21-003
N (%) of Subjects	14 (11)	24 (19)	40 (40)	69 (33)	68 (33)
General system disorders NEC	9 (7)	14 (11)	33 (33)	58 (28)	58 (28)
Administration site reactions	1 (<1)	2 (2)	6 (6)	1 (<1)	1 (<1)
Asthenic conditions	1 (<1)	2 (2)	6 (6)	1 (<1)	1 (<1)
Fatigue	1 (<1)	2 (2)	6 (6)	1 (<1)	1 (<1)
Injection site induration	0	0	4 (4)	9 (4)	27 (13)
Injection site pain	0	0	4 (4)	9 (4)	27 (13)
Injection site reactions	0	0	4 (4)	9 (4)	27 (13)
General signs and symptoms NEC	1 (<1)	0	3 (3)	12 (6)	24 (12)
Infections and infestations	5 (4)	10 (8)	24 (24)	47 (22)	48 (23)
Bacterial infectious disorders	0	0	7 (7)	18 (9)	21 (10)
Infections - pathogen unspecified	6 (5)	9 (7)	6 (6)	12 (6)	18 (9)
Upper respiratory tract infections	2 (2)	1 (<1)	8 (8)	42 (20)	31 (15)
Nasopharyngitis	1 (<1)	1 (<1)	3 (3)	31 (15)	20 (10)
Upper respiratory tract infection	2 (2)	1 (<1)	8 (8)	42 (20)	31 (15)
Viral infectious disorders	1 (<1)	0	2 (2)	4 (2)	13 (6)
Injury, poisoning and procedural complications	2 (2)	7 (6)	4 (4)	14 (7)	39 (19)
Injuries NEC	2 (2)	7 (6)	4 (4)	13 (6)	37 (18)

Week 0 through 24

Most Frequently Reported (>=5% in any Group) Adverse Events in Combined ISS

Preferred Term (MedDRA)	Placebo ALK21-013	VIVITROL ALK21-013	VIVITROL ALK21-006 Opiod Only	Placebo ALK21-003	VIVITROL ALK21-003
System Organ Class (MedDRA)	0	0	2 (2)	16 (8)	12 (6)
High Level Group Term (MedDRA)	12 (10)	26 (21)	20 (20)	37 (18)	26 (13)
High Level Term (MedDRA)	1 (<1)	3 (2)	7 (7)	6 (3)	2 (<1)
Non-site specific injuries NEC	1 (<1)	3 (2)	6 (6)	6 (3)	2 (<1)
Investigations	10 (8)	24 (19)	5 (5)	10 (5)	7 (3)
Enzyme investigations NEC	10 (8)	24 (19)	5 (5)	10 (5)	7 (3)
Skeletal and cardiac muscle analyses	7 (6)	16 (13)	3 (3)	2 (<1)	2 (<1)
Blood creatine phosphokinase increased	3 (2)	13 (10)	2 (2)	2 (<1)	3 (1)
Liver function analyses -	4 (3)	9 (7)	1 (<1)	7 (3)	4 (2)
Alanine aminotransferase increased	0	1 (<1)	6 (6)	10 (5)	5 (2)
Aspartate aminotransferase increased	0	1 (<1)	6 (6)	10 (5)	5 (2)
Gamma-glutamyltransferase increased	0	1 (<1)	6 (6)	11 (5)	39 (19)
Physical examination topics	0	1 (<1)	6 (6)	7 (3)	34 (17)
Physical examination procedures	0	1 (<1)	6 (6)	7 (3)	34 (17)
Metabolism and nutrition disorders					
Appetite and general nutritional disorders					
Appetite disorders					

N (%) of Subjects

Week 0 through 24

Most Frequently Reported (>=5% in any Group) Adverse Events in Combined ISS

Preferred Term (MedDRA)	Placebo ALK21-013	VIVITROL ALK21-013	VIVITROL ALK21-006 Opiod Only	Placebo ALK21-003	VIVITROL ALK21-003
System Organ Class (MedDRA)	0	0	3 (3)	3 (1)	26 (13)
High Level Group Term (MedDRA)	4 (3)	4 (3)	22 (22)	48 (23)	63 (31)
High Level Term (MedDRA)	1 (<1)	0	3 (3)	13 (6)	22 (11)
Musculoskeletal and connective tissue disorders	1 (<1)	0	3 (3)	10 (5)	21 (10)
Decreased appetite	1 (<1)	0	2 (2)	9 (4)	18 (9)
Joint disorders	2 (2)	0	10 (10)	15 (7)	28 (14)
Joint related signs and symptoms	0	0	6 (6)	11 (5)	10 (5)
Myalgia	0	0	6 (6)	11 (5)	10 (5)
Muscle pains	1 (<1)	0	4 (4)	4 (2)	16 (8)
Myalgia	1 (<1)	2 (2)	12 (12)	23 (11)	28 (14)
Muscle related signs and symptoms NEC	1 (<1)	2 (2)	12 (12)	23 (11)	28 (14)
Musculoskeletal and connective tissue disorders NEC	1 (<1)	2 (2)	6 (6)	10 (5)	10 (5)
Musculoskeletal and connective tissue signs and symptoms NEC	0	0	3 (3)	7 (3)	13 (6)
Back pain	4 (3)	5 (4)	32 (32)	59 (28)	79 (39)
Nervous system disorders	3 (2)	4 (3)	17 (17)	39 (19)	49 (24)
Pain in extremity	3 (2)	4 (3)	14 (14)	38 (18)	48 (23)
Headaches	3 (2)	4 (3)	11 (11)	34 (16)	47 (23)
Headaches NEC					
Headache					

N (%) of Subjects

Week 0 through 24

Most Frequently Reported (>=5% in any Group) Adverse Events in Combined ISS

System Organ Class (MedDRA) High Level Group Term (MedDRA) High Level Term (MedDRA) Preferred Term (MedDRA)	Placebo ALK21-013	VIVITROL ALK21-013	VIVITROL ALK21-006 Opiod Only	Placebo ALK21-003	VIVITROL ALK21-003
	0	0	11 (11)	23 (11)	44 (21)
	0	0	6 (6)	5 (2)	12 (6)
	0	0	3 (3)	8 (4)	26 (13)
	0	0	3 (3)	8 (4)	26 (13)
Neurological disorders NEC	5 (4)	9 (7)	34 (34)	58 (28)	81 (40)
Disturbances in consciousness NEC	0	1 (<1)	6 (6)	17 (8)	23 (11)
Neurological signs and symptoms NEC	0	1 (<1)	6 (6)	17 (8)	22 (11)
Dizziness	0	1 (<1)	4 (4)	15 (7)	20 (10)
Psychiatric disorders	0	0	8 (8)	9 (4)	17 (8)
Anxiety disorders and symptoms	0	0	7 (7)	8 (4)	16 (8)
Anxiety	0	0	7 (7)	8 (4)	16 (8)
Anxiety symptoms	0	0	3 (3)	4 (2)	12 (6)
Depressed mood disorders and disturbances	0	0	2 (2)	4 (2)	11 (5)
Depressive disorders	0	0	2 (2)	2 (<1)	11 (5)
Depression	1 (<1)	8 (6)	14 (14)	26 (12)	33 (16)
Sexual dysfunctions, disturbances and gender identity disorders	1 (<1)	8 (6)	13 (13)	25 (12)	28 (14)
Sexual desire disorders	1 (<1)	8 (6)	13 (13)	25 (12)	28 (14)
Libido decreased	1 (<1)	8 (6)	13 (13)	25 (12)	28 (14)
Disturbances in initiating and maintaining sleep	0	0	4 (4)	5 (2)	15 (7)
Insomnia	0	0	4 (4)	5 (2)	15 (7)

N (%) of Subjects

Week 0 through 24

Most Frequently Reported (>=5% in any Group) Adverse Events in Combined ISS

Preferred Term (MedDRA)	Placebo ALK21-013	VIVITROL ALK21-013	VIVITROL ALK21-006 Opiod Only	Placebo ALK21-003	VIVITROL ALK21-003
System Organ Class (MedDRA)					
High Level Group Term (MedDRA)	1 (<1)	2 (2)	12 (12)	17 (8)	28 (14)
High Level Term (MedDRA)	1 (<1)	2 (2)	7 (7)	15 (7)	17 (8)
Respiratory, thoracic and mediastinal disorders	4 (3)	2 (2)	8 (8)	19 (9)	27 (13)
Respiratory disorders NEC	3 (2)	2 (2)	4 (4)	14 (7)	17 (8)
Skin and subcutaneous tissue disorders					
Epidermal and dermal conditions					

Table 5.3.5.3.9.1

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N (%) of Subjects

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

ETHNIC FACTORS IN THE ACCEPTABILITY OF FOREIGN CLINICAL DATA
E5(R1)

Current *Step 4* version

dated 5 February 1998

(including the Post Step 4 corrections agreed by the Steering Committee on 11 March 1998)

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

E5(R1)
Document History

First Codification	History	Date	New Codification **November 2005**
E5	Approval by the Steering Committee under *Step 2* and release for public consultation.	5 March 1997	E5
E5	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	5 February 1998	E5

Current *Step 4* version

E5	Approval by the Steering Committee of minor *Post-Step 4* editorial corrections.	11 March 1998	E5(R1)

In order to facilitate the implementation of the E5 guideline, the ICH Experts have developed a series of Q&As which can be downloaded from the ICH web site directly from the following url : http://www.ich.org

E5 Questions & Answers History
Current E5 Q&As posted on the web site

E5 Q&As	Approval by the Steering Committee	November 2003	E5 Q&As

ETHNIC FACTORS IN THE ACCEPTABILITY OF FOREIGN CLINICAL DATA

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 5 February 1998, this guideline is recommended for adoption to the three regulatory parties to ICH

(This document includes the Post Step 4 corrections agreed by the Steering Committee on 11 March 1998)

TABLE OF CONTENTS

ETHNIC FACTORS IN THE ACCEPTABILITY OF FOREIGN CLINICAL DATA

1. INTRODUCTION

The purpose of this guidance is to facilitate the registration of medicines among ICH regions* (see Glossary) by recommending a framework for evaluating the impact of ethnic factors* upon a medicine's effect, i.e., its efficacy and safety at a particular dosage* and dose regimen*. It provides guidance with respect to regulatory and development strategies that will permit adequate evaluation of the influence of ethnic factors while minimizing duplication of clinical studies and supplying medicines expeditiously to patients for their benefit. This guidance should be implemented in context with the ICH guidances. For the purposes of this document, ethnic factors are defined as those factors relating to the genetic and physiologic (intrinsic*) and the cultural and environmental (extrinsic*) characteristics of a population (Appendix A).

1.1 Objectives

- To describe the characteristics of foreign clinical data that will facilitate their extrapolation to different populations and support their acceptance as a basis for registration of a medicine in a new region*.
- To describe regulatory strategies that minimize duplication of clinical data and facilitate acceptance of foreign clinical data in the new region.
- To describe the use of bridging studies*, when necessary, to allow extrapolation of foreign clinical data to a new region.
- To describe development strategies capable of characterizing ethnic factor influences on safety, efficacy, dosage and dose regimen.

1.2 Background

All regions acknowledge the desirability of utilizing foreign clinical data that meet the regulatory standards and clinical trial practices acceptable to the region considering the application for registration.

However, concern that ethnic differences may affect the medication's safety, efficacy, dosage and dose regimen in the new region has limited the willingness to rely on foreign clinical data. Historically, this has been one of the reasons, therefore, the regulatory authority in the new region has often requested that all, or much of, the foreign clinical data in support of registration be duplicated in the new region. Although ethnic differences among populations may cause differences in a medicine's safety, efficacy, dosage or dose regimen, many medicines have comparable characteristics and effects across regions. Requirements for extensive duplication of clinical evaluation for every compound can delay the availability of new therapies and unnecessarily waste drug development resources.

1.3 Scope

This guidance is based on the premise that it is not necessary to repeat the entire clinical drug development program in the new region and is intended to recommend strategies for accepting foreign clinical data as full or partial support for approval of an application in a new region. It is critical to appreciate that this guidance is not intended to alter the data requirements for registration in the new region; it seeks to recommend when these data requirements may be satisfied with foreign clinical data. All data in the clinical data package, including foreign data, should meet the

standards of the new region with respect to study design and conduct and the available data should satisfy the regulatory requirements in the new region. Additional studies conducted in any region may be required by the new region to complete the clinical data package.

Once a clinical data package fulfils the regulatory requirements of the new region, the only remaining issue with respect to the acceptance of the foreign clinical data is its ability to be extrapolated to the population of the new region. When the regulatory authority or the sponsor is concerned that differences in ethnic factors could alter the efficacy or safety of the medicine in the population in the new region, the sponsor may need to generate a limited amount of clinical data in the new region in order to extrapolate or "bridge" the clinical data between the two regions.

If a sponsor needs to obtain additional clinical data to fulfil the regulatory requirements of the new region, it is possible that these clinical trials can be designed to also serve as the bridging studies.

Thus, the sponsor and the regional regulatory authority of the new region would assess an application for registration for:

1. its completeness with respect to the regulatory requirements of the new region; and

2. the ability to extrapolate to the new region those parts of the application (which could be most or all of the application) based on studies from the foreign region (Appendix B).

2. ASSESSMENT OF THE CLINICAL DATA PACKAGE INCLUDING FOREIGN CLINICAL DATA FOR ITS FULFILMENT OF REGULATORY REQUIREMENTS IN THE NEW REGION

The regional regulatory authority would assess the clinical data package, including the foreign data, as to whether or not it meets all of the regulatory standards regarding the nature and quality of the data, irrespective of its geographic origin, i.e., data generated either totally in a foreign region (or regions) or data from studies conducted both in a foreign and the new region to which the application is being made. A clinical data package that meets all of these regional regulatory requirements is defined as a "Complete" Clinical Data Package* for submission and potential approval. The acceptability of the foreign clinical data component of the complete data package depends then upon whether it can be extrapolated to the population of the new region.

Before extrapolation can be considered, the Complete Clinical Data Package, including foreign clinical data, submitted to the new region should contain:

- Adequate characterization of pharmacokinetics*, pharmacodynamics*, dose-response, efficacy and safety in the population of the foreign region(s).
- Clinical trials establishing dose response, efficacy and safety. These trials should:
    - Be designed and conducted according to regulatory standards in the new region, e.g., choice of controls, and should be conducted according to GCP
    - Be adequate and well-controlled*
    - Utilize endpoints that are considered appropriate for assessment of treatment
    - Evaluate clinical disorders using medical and diagnostic definitions that are acceptable to the new region.

- Characterization in a population relevant to the new region of the pharmacokinetics, and where possible, pharmacodynamics and dose response for pharmacodynamic endpoints. This characterization could be performed in the foreign region in a population representative of the new region* or in the new region*.

Several ICH guidelines that address aspects of design, conduct, analysis and reporting of clinical trials will help implement the concepts of the Complete Clinical Data Package. These guidances include GCP's (E6), evaluation of dose response (E4), adequacy of safety data (E1 and E2), conduct of studies in the elderly (E7), reporting of study results (E3), general considerations for clinical trials (E8), and statistical considerations (E9). A guidance on the choice of control group in clinical trials (E10) is under development.

2.1 Additional Studies to Meet the New Region's Regulatory Requirements

When the foreign clinical data do not meet the regional regulatory requirements, the regulatory authority may require additional clinical trials such as:

- clinical trials in different subsets of the population such as patients with renal insufficiency, patients with hepatic dysfunction, etc.
- clinical trials using different comparators at the new region's approved dosage and dose regimen
- drug-drug interaction studies

3. ASSESSMENT OF THE FOREIGN CLINICAL DATA FOR EXTRAPOLATION TO THE NEW REGION

3.1 Characterization of the Medicine's Sensitivity to Ethnic Factors

To assess a medicine's sensitivity to ethnic factors it is important that there be knowledge of its pharmacokinetic and pharmacodynamic properties and the translation of those properties to clinical effectiveness and safety. A reasonable evaluation is described in Appendix C. Some properties of a medicine (chemical class, metabolic pathway, pharmacologic class) make it more or less likely to be affected by ethnic factors (Appendix D). Characterization of a medicine as "ethnically insensitive", i.e., unlikely to behave differently in different populations, would usually make it easier to extrapolate data from one region to another and need less bridging data.

Factors that make a medicine ethnically sensitive or insensitive will become better understood and documented as effects in different regions are compared. It is clear at present, however, that such characteristics as clearance by an enzyme showing genetic polymorphism and a steep dose-response curve will make ethnic differences more likely. Conversely, a lack of metabolism or active excretion, a wide therapeutic dose range*, and a flat dose response curve will make ethnic differences less likely. The clinical experience with other members of the drug class in the new region will also contribute to the assessment of the medicine's sensitivity to ethnic factors. It may be easier to conclude that the pharmacodynamic and clinical behaviour of a medicine will be similar in the foreign and new regions if other members of the pharmacologic class have been studied and approved in the new region with dosing regimens similar to those used in the original region.

3.2 Bridging Data Package

3.2.1 Definition of Bridging Data Package and Bridging Study

A bridging data package consists of: 1) selected information from the Complete Clinical Data Package that is relevant to the population of the new region, including pharmacokinetic data, and any preliminary pharmacodynamic and dose-response data, and 2) if needed, a bridging study to extrapolate the foreign efficacy data and/or safety data to the new region.

A bridging study is defined as a study performed in the new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage and dose regimen in the new region that will allow extrapolation of the foreign clinical data to the population in the new region. A bridging study for efficacy could provide additional pharmacokinetic information in the population of the new region. When no bridging study is needed to provide clinical data for efficacy, a pharmacokinetic study in the new region may be considered as a bridging study.

3.2.2 Nature and Extent of the Bridging Study

This guidance proposes that when the regulatory authority of the new region is presented with a clinical data package that fulfils its regulatory requirements, the authority should request only those additional data necessary to assess the ability to extrapolate foreign data from the Complete Clinical Data Package to the new region. The sensitivity of the medicine to ethnic factors will help determine the amount of such data. In most cases, a single trial that successfully provides these data in the new region and confirms the ability to extrapolate data from the original region should suffice and should not need further replication. Note that even though a single study should be sufficient to "bridge" efficacy data, a sponsor may find it practical to obtain the necessary data by conducting more than one study. For example, where it is intended that a fixed dose, dose-response study using a clinical endpoint is needed as the bridging study, a short-term pharmacologic endpoint study may be used to choose the dose(s) for the larger (clinical endpoint) study.

When the regulatory authority requests, or the sponsor decides to conduct, a bridging study, discussion between the regional regulatory authority and sponsor is encouraged, when possible, to determine what kind of bridging study will be needed. The relative ethnic sensitivity will help determine the need for and the nature of the bridging study. For regions with little experience with registration based on foreign clinical data, the regulatory authorities may still request a bridging study for approval even for compounds insensitive to ethnic factors. As experience with interregional acceptance increases, there will be a better understanding of situations in which bridging studies are needed. It is hoped that with experience, the need for bridging data will lessen.

The following is general guidance about the ability to extrapolate data generated from a bridging study:

- If the bridging study shows that dose response, safety and efficacy in the new region are similar, then the study is readily interpreted as capable of "bridging" the foreign data.
- If a bridging study, properly executed, indicates that a different dose in the new region results in a safety and efficacy profile that is not substantially different from that derived in the original region, it will often be possible to extrapolate the foreign data to the new region, with appropriate dose adjustment, if this can be adequately justified (e.g., by pharmacokinetic and/or pharmacodynamic data).

- If the bridging study designed to extrapolate the foreign data is not of sufficient size to confirm adequately the extrapolation of the adverse event profile to the new population, additional safety data may be necessary (section 3.2.4).
- If the bridging study fails to verify safety and efficacy, additional clinical data (e.g., confirmatory clinical trials) would be necessary.

3.2.3 Bridging Studies for Efficacy

Generally, for medicines characterized as insensitive to ethnic factors, the type of bridging study needed (if needed) will depend upon experience with the drug class and upon the likelihood that extrinsic ethnic factors (including design and conduct of clinical trials) could affect the medicine's safety, efficacy, and dose-response. For medicines that are ethnically sensitive, a bridging study may often be needed if the populations in the two regions are different. The following examples illustrate types of bridging studies for consideration in different situations:

- ***No Bridging Study***

In some situations, extrapolation of clinical data may be feasible without a bridging study:

If the medicine is ethnically insensitive and extrinsic factors such as medical practice and conduct of clinical trials in the two regions are generally similar.

If the medicine is ethnically sensitive but the two regions are ethnically similar and there is sufficient clinical experience with pharmacologically related compounds to provide reassurance that the class behaves similarly in patients in the two regions with respect to efficacy, safety, dosage and dose regimen. This might be the case for well-established classes of drugs known to be administered similarly but not necessarily identically in the two regions.

- ***Bridging Studies using pharmacologic endpoints***

If the regions are ethnically dissimilar and the medicine is ethnically sensitive but extrinsic factors are generally similar (e.g., medical practice, design and conduct of clinical trials) and the drug class is a familiar one in the new region, a controlled pharmacodynamic study in the new region, using a pharmacologic endpoint that is thought to reflect relevant drug activity (which could be a well-established surrogate endpoint) could provide assurance that the efficacy, safety, dose and dose regimen data developed in the first region are applicable to the new region. Simultaneous pharmacokinetic (i.e., blood concentration) measurements may make such studies more interpretable.

- ***Controlled Clinical Trials***

It will usually be necessary to carry out a controlled clinical trial, often a randomized, fixed dose, dose-response study, in the new region when:

1. there are doubts about the choice of dose,
2. there is little or no experience with acceptance of controlled clinical trials carried out in the foreign region,
3. medical practice, e.g., use of concomitant medications and design and/or conduct of clinical trials are different, or

4 the drug class is not a familiar one in the new region.

Depending on the situation, the trial could replicate the foreign study or could utilize a standard clinical endpoint in a study of shorter duration than the foreign studies or

utilize a validated surrogate endpoint, e.g., blood pressure or cholesterol (longer studies and other endpoints may have been used in the foreign phase III clinical trials).

If pharmacodynamic data suggest that there are interregional differences in response, it will generally be necessary to carry out a controlled trial with clinical endpoints in the new region. Pharmacokinetic differences may not always create that necessity, as dosage adjustments in some cases might be made without new trials. However, any substantial difference in metabolic pattern may often indicate a need for a controlled clinical trial.

When the practice of medicine differs significantly in the use of concomitant medications, or adjunct therapy could alter the medicine's efficacy or safety, the bridging study should be a controlled clinical trial.

3.2.4 Bridging Studies for Safety

Even though the foreign clinical data demonstrate efficacy and safety in the foreign region, there may occasionally remain a safety concern in the new region. Safety concerns could include the accurate determination of the rates of relatively common adverse events in the new region and the detection of serious adverse events (in the 1% range and generally needing about 300 patients to assess). Depending upon the nature of the safety concern, safety data could be obtained in the following situations:

- A bridging study to assess efficacy, such as a dose-response study, could be powered to address the rates of common adverse events and could also allow identification of serious adverse events that occur more commonly in the new region. Close monitoring of such a trial would allow recognition of such serious events before an unnecessarily large number of patients in the new region is exposed. Alternatively, a small safety study could precede the bridging study to provide assurance that serious adverse effects were not occurring at a high rate.
    - If there is no efficacy bridging study needed or if the efficacy bridging study is too small or of insufficient duration to provide adequate safety information, a separate safety study may be needed. This could occur where there is:
    - an index case of a serious adverse event in the foreign clinical data
    - a concern about differences in reporting adverse events in the foreign region
    - only limited safety data in the new region arising from an efficacy bridging study, inadequate to extrapolate important aspects of the safety profile, such as rates of common adverse events or of more serious adverse events

4. DEVELOPMENTAL STRATEGIES FOR GLOBAL DEVELOPMENT

Definition of not only pharmacokinetics but also pharmacodynamics and dose response early in the development program may facilitate the determination of the need for, and nature of, any requisite bridging data. Any candidate medicine for global development should be characterized as ethnically sensitive or insensitive (Appendix D). Ideally, this characterization should be conducted during the early clinical phases of drug development, i.e., human pharmacology and therapeutic exploratory studies. In some cases, it may be useful to discuss bridging study designs with regulatory agencies prior to completion of the clinical data package. However, analysis of the data within the Complete Clinical Data Package will determine the need for, and type of bridging study. For global development, studies should include populations representative of the regions where the medicine is to be registered and should be conducted according to ICH guidelines.

A sponsor may wish to leave the assessment of pharmacokinetics, pharmacodynamics, dosage and dose regimens in populations relevant to the new region until later in the drug development program. Pharmacokinetic assessment could be accomplished by formal pharmacokinetic studies or by applying population pharmacokinetic methods to clinical trials conducted either in a population relevant to the new region, or in the new region.

5. SUMMARY

This guidance describes how a sponsor developing a medicine for a new region can deal with the possibility that ethnic factors could influence the effects (safety and efficacy) of medicines and the risk/benefit assessment in different populations. Results from the foreign clinical trials could comprise most, or in some cases, all of the clinical data package for approval in the new region, so long as they are carried out according to the requirements of the new region. Acceptance in the new region of such foreign clinical data may be achieved by generating "bridging" data in order to extrapolate the safety and efficacy data from the population in the foreign region(s) to the population in the new region.

GLOSSARY

Adequate and Well-controlled Trial

An adequate and well controlled trial has the following characteristics:

- a design that permits a valid comparison with a control to provide a quantitative assessment of treatment effect;
- the use of methods to minimize bias in the allocation of patients to treatment groups and in the measurement and assessment of response to treatment; and
- an analysis of the study results appropriate to the design to assess the effects of the treatment.

Bridging Data Package

Selected information from the Complete Clinical Data Package that is relevant to the population of the new region, including pharmacokinetic data, and any preliminary pharmacodynamic and dose-response data and, if needed, supplemental data obtained from a bridging study in the new region that will allow extrapolation of the foreign safety and efficacy data to the population of the new region.

Bridging Study

A bridging study is defined as a supplemental study performed in the new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage and dose regimen in the new region that will allow extrapolation of the foreign clinical data to the new region. Such studies could include additional pharmacokinetic information.

Complete Clinical Data Package

A clinical data package intended for registration containing clinical data that fulfil the regulatory requirements of the new region and containing pharmacokinetic data relevant to the population in the new region.

Compounds Insensitive to Ethnic Factors

A compound whose characteristics suggest minimal potential for clinically significant impact by ethnic factors on safety, efficacy, or dose response.

Compounds Sensitive to Ethnic Factors

A compound whose pharmacokinetic, pharmacodynamic, or other characteristics suggest the potential for clinically significant impact by intrinsic and/or extrinsic ethnic factors on safety, efficacy, or dose response.

Dosage

The quantity of a medicine given per administration, or per day.

Dose Regimen

The route, frequency and duration of administration of the dose of a medicine over a period of time.

Ethnic Factors

The word ethnicity is derived from the Greek word "ethnos", meaning nation or people. Ethnic factors are factors relating to races or large populations grouped according to common traits and customs. Note that this definition gives ethnicity, by virtue of its cultural as well as genetic implications, a broader meaning than racial. Ethnic factors may be classified as either intrinsic or extrinsic. (Appendix A)

- **Extrinsic Ethnic Factors:**

  Extrinsic ethnic factors are factors associated with the environment and culture in which a person resides. Extrinsic factors tend to be less genetically and more culturally and behaviourally determined. Examples of extrinsic factors include the social and cultural aspects of a region such as medical practice, diet, use of tobacco, use of alcohol, exposure to pollution and sunshine, socio-economic status, compliance with prescribed medications, and, particularly important to the reliance on studies from a different region, practices in clinical trial design and conduct.

- **Intrinsic Ethnic Factors:**

  Intrinsic ethnic factors are factors that help to define and identify a sub-population and may influence the ability to extrapolate clinical data between regions. Examples of intrinsic factors include genetic polymorphism, age, gender, height, weight, lean body mass, body composition, and organ dysfunction.

Extrapolation of Foreign Clinical Data

The generalization and application of the safety, efficacy and dose response data generated in a population of a foreign region to the population of the new region.

Foreign Clinical Data

Foreign clinical data is defined as clinical data generated outside of the new region (i.e., in the foreign region).

ICH Regions

European Union, Japan, The United States of America.

New Region

The region where product registration is sought.

Population Representative of the New Region

A population that includes the major racial groups within the new region.

Pharmacokinetic Study

A study of how a medicine is handled by the body, usually involving measurement of blood concentrations of drug and its metabolite(s) (sometimes concentrations in urine or tissues) as a function of time. Pharmacokinetic studies are used to characterize absorption, distribution, metabolism and excretion of a drug, either in blood or in other pertinent locations. When combined with pharmacodynamic measures (a PK/PD study) it can characterize the relation of blood concentrations to the extent and timing of pharmacodynamic effects.

Pharmacodynamic Study

A study of a pharmacological or clinical effect of the medicine in individuals to describe the relation of the effect to dose or drug concentration. A pharmacodynamic effect can be a potentially adverse effect (anticholinergic effect with a tricyclic), a measure of activity thought related to clinical benefit (various measures of beta-blockade, effect on ECG intervals, inhibition of ACE or of angiotensin I or II response), a short term desired effect, often a surrogate endpoint (blood pressure, cholesterol), or the ultimate intended clinical benefit (effects on pain, depression, sudden death).

Population Pharmacokinetic Methods

Population pharmacokinetic methods are a population-based evaluation of measurements of systemic drug concentrations, usually two or more per patient under steady state conditions, from all, or a defined subset of, patients who participate in clinical trials.

Therapeutic Dose Range

The difference between the lowest effective dose and the highest dose that gives further benefit.

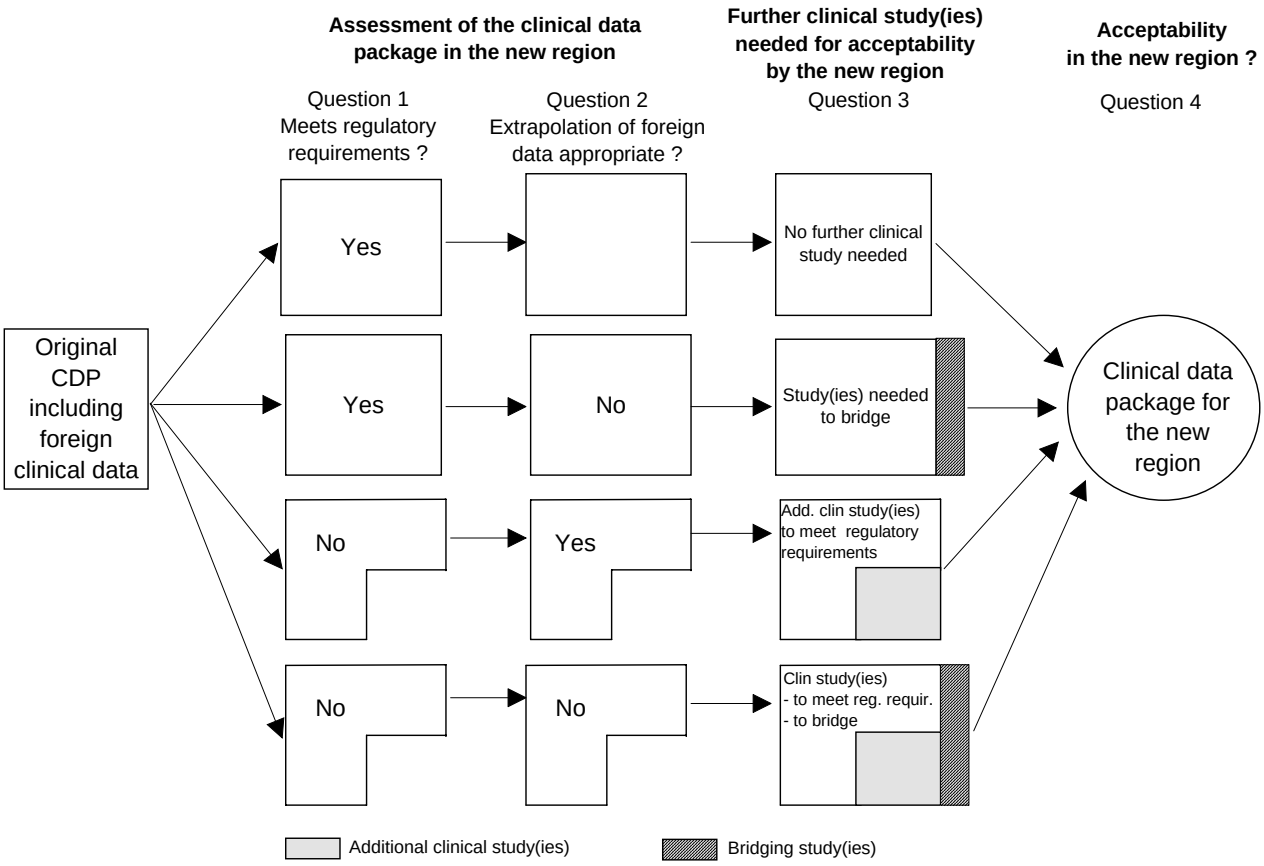
APPENDIX A

Classification of intrinsic and extrinsic ethnic factors

INTRINSIC		EXTRINSIC
Genetic	Physiological and pathological conditions	Environmental
	Age	Climate
Gender	(children-elderly)	Sunlight
	Height	Pollution
	Bodyweight	
	Liver	**Culture**
	Kidney	Socioeconomic factors
	Cardiovascular functions	Educational status
	ADME	Language
	Receptor sensitivity	
Race		Medical practice
		Disease definition/Diagnostic
Genetic polymorphism of the drug metabolism		Therapeutic approach
		Drug compliance
		Smoking
		Alcohol
		Food habits
Genetic diseases	Diseases	Stress
		Regulatory practice/GCP
		Methodology/Endpoints

APPENDIX B

Assessment of the clinical data package (CDP) for acceptability



APPENDIX C

Pharmacokinetic, Pharmacodynamic, and Dose Response Considerations

Evaluation of the pharmacokinetics and pharmacodynamics, and their comparability, in the three major racial groups most relevant to the ICH regions (Asian, Black, and Caucasian) is critical to the registration of medicines in the ICH regions. Basic pharmacokinetic evaluation should characterize absorption, distribution, metabolism, excretion (ADME), and where appropriate, food-drug and drug-drug interactions.

Adequate pharmacokinetic comparison between populations of the two regions allows rational consideration of what kinds of further pharmacodynamic and clinical studies (bridging studies) are needed in the new region. In contrast to the pharmacokinetics of a medication, where differences between populations may be attributed primarily to intrinsic ethnic factors and are readily identified, the pharmacodynamic response (clinical effectiveness, safety, and dose-response) may be influenced by both intrinsic and extrinsic ethnic factors and this may be difficult to identify except by conducting clinical studies in the new region.

The ICH-E4 document describes various approaches to dose-response evaluation. In general, dose-response (or concentration response) should be evaluated for both pharmacologic effect (where one is considered pertinent) and clinical endpoints in the foreign region. The pharmacologic effect, including dose-response, may also be evaluated in the foreign region in a population representative of the new region. Depending on the situation, data on clinical efficacy and dose-response in the new region may or may not be needed, e.g., if the drug class is familiar and the pharmacologic effect is closely linked to clinical effectiveness and dose-response, these foreign pharmacodynamic data may be a sufficient basis for approval and clinical endpoint and dose-response data may not be needed in the new region. The pharmacodynamic evaluation, and possible clinical evaluation (including dose-response) is important because of the possibility that the response curve may be shifted in a new population. Examples of this are well-documented, e.g., the decreased response in blood pressure of blacks to angiotensin-converting enzyme inhibitors.

APPENDIX D

A Medicine's Sensitivity to Ethnic Factors

Characterization of a medicine according to the potential impact of ethnic factors upon its pharmacokinetics, pharmacodynamics and therapeutic effects may be useful in determining what sort of bridging study is needed in the new region. The impact of ethnic factors upon a medicine's effect will vary depending upon the drug's pharmacologic class and indication and the age and gender of the patient. No one property of the medicine is predictive of the compound's relative sensitivity to ethnic factors. The type of bridging study needed is ultimately a matter of judgement but assessment of sensitivity to ethnic factors may help in that judgement.

The following properties of a compound make it less likely to be sensitive to ethnic factors:

- Linear pharmacokinetics (pK)
- A flat pharmacodynamic (PD) (effect-concentration) curve for both efficacy and safety in the range of the recommended dosage and dose regimen (this may mean that the medicine is well-tolerated)
- A wide therapeutic dose range* (again, possibly an indicator of good tolerability)
- Minimal metabolism or metabolism distributed among multiple pathways
- High bioavailability, thus less susceptibility to dietary absorption effects
- Low potential for protein binding
- Little potential for drug-drug, drug-diet and drug-disease interactions
- Non-systemic mode of action
- Little potential for inappropriate use

The following properties of a compound make it more likely to be sensitive to ethnic factors:

- Non-linear pharmacokinetics
- A steep pharmacodynamic curve for both efficacy and safety (a small change in dose results in a large change in effect) in the range of the recommended dosage and dose regimen
- A narrow therapeutic dose range
- Highly metabolized, especially through a single pathway, thereby increasing the potential for drug-drug interaction
- Metabolism by enzymes known to show genetic polymorphism
- Administration as a prodrug, with the potential for ethnically variable enzymatic conversion
- High inter-subject variation in bioavailability
- Low bioavailability, thus more susceptible to dietary absorption effects
- High likelihood of use in a setting of multiple co-medications
- High likelihood for inappropriate use , e.g., analgesics and tranquilizers.

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

E5 Implementation Working Group
Questions & Answers (R1)

Current version
dated June 2, 2006

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In order to facilitate the implementation of the E5 guideline, the ICH Experts have developed a series of Q&As:

E5 Q&As
Document History

First Codification	History	Date	New Codification November 2005
E5 Q&As	Approval by the ICH Steering Committee	11 November 2003	E5 Q&As
E5 Q&As	Approval by the ICH Steering Committee of the newly added question	2 June 2006	E5 Q&As (R1)

In November 2005, the ICH Steering Committee adopted a new codification system for ICH Guidelines. The purpose of this new codification is to ensure that the numbering / coding of ICH Guidelines is more logical, consistent and clearer. Because the new system applies to existing as well as new ICH Guidelines a history box has been added to the beginning of all Guidelines to explain how the Guideline was developed and what is the latest version.

With the new codification revisions to an ICH Guideline are shown as (R1), (R2), (R3) depending on the number of revisions. Annexes or Addenda to Guidelines have now been incorporated into the core Guidelines and are indicated as revisions to the core Guideline (e.g., R1).

For better comprehension of the E5 references within the text, please see below the document change history for E5 guideline.

E5
Document History

First Codification	History	Date	New Codification **November 2005**
E5	Approval by the Steering Committee under *Step 2* and release for public consultation.	5 March 1997	E5
E5	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	5 February 1998	E5

Current *Step 4* version

E5	Approval by the Steering Committee of minor *Post-Step 4* editorial corrections.	11 March 1998	E5(R1)

E5 Ethnic Factors : Questions and Answers

	Date of Approval	Questions	Answers
1	**Nov. 2003**	I am planning to develop my new drug globally. Does E5 provide guidance for this approach?	E5 does provide some guidance in this situation. E5 addresses primarily how development programs in one or two regions might support approval in another region. E5 says, in general, that if the data developed in one region satisfy the requirements for evidence in a new region, but there is a concern about possible intrinsic or extrinsic ethnic differences between the two regions, then it should be possible to extrapolate the data to the new region with a single bridging study. The bridging study could be a pharmacodynamic study or a full clinical trial, possibly a dose-response study. The bridging study would allow extrapolation of an adequate data base to the new region. It would seem possible, and efficient, to assess potential regional differences as part of a global development program, i.e. for development of data to occur simultaneously in various regions, rather than sequentially. For example, if multi-regional trials had a sufficient number of trial subjects from the new region, it might be possible to analyze the impact of ethnic differences in those studied, to determine whether the entire data base is pertinent to the new region. The basic issues to be considered in a global study design that could affect a region's willingness to rely on these data are: a) definition and diagnoses of disease condition and patient, b) choice of control group, c) regional target or objective of treatment with choice of efficacy variables, d) methods of assessment of safety, e) medical practice, f) duration of the trial, g) regional concomitant medications, h) severity distribution of eligible subjects, and i) similarity of dose and dose regimens. To determine whether your proposed global program will address the requirements of a specific region, it is recommended that early consultation and discussions be held with regulatory authorities in that region.

E5 Ethnic Factors : Questions and Answers

Date of Approval		Questions	Answers
2	**Nov. 2003**	I have developed my drug in one region, addressing safety, efficacy, dosing, etc., as well as use in special populations such as patients with renal/hepatic impairment, the elderly, children, and pregnant and lactating women. If I can successfully demonstrate (e.g. through a bridging study) that my safety, efficacy and dosing information in the general population are relevant to the new region, will I also need to further address the extrapolatability of the special population data?	In general, if the studies of special populations are sufficient in design (e.g. include an appropriate range of severity of impairment) to address regulatory requirements of the new region, but are conducted in a foreign region, and if evidence supports the extrapolation of the data in the general population to the new region, you will probably not need to address the issue of special populations again in the new region. Note, however, that for a new indication in a special population (e.g. pediatric depression) a region might require a separate bridging study.
3	**Nov. 2003**	I believe that my drug is sensitive to ethnic factors and that the medical settings in which it is used may vary among regions. Does this mean that my efficacy study in one region is of no value in support of my application in another?	No. Assuming the new region finds the studies in the first region pertinent, the regulatory authority of the new region will likely require a controlled study in its own region to establish efficacy (and/or to address other issues). E5 indicates, however, that the second region would be likely to consider a single such study adequate if the data from the foreign region otherwise meet all the requirements of the new region. If the new study supports the same conclusions as the study(ies) in the original region, no further confirmation should be needed, as the data from the original region would likely be considered to confirm the finding in the new region. In that case, the study in the new region need not necessarily have the identical dose and treatment effect size to confirm the findings from the initial region. There might also be situations in which the region would consider further safety data necessary. For example, if the new region considered a higher dose or more frequent dosing necessary and if this finding were not a pharmacokinetic effect, sponsors might need to provide additional safety data.

E5 Ethnic Factors : Questions and Answers

Date of Approval		Questions	Answers
4	**Nov. 2003**	I believe that my drug is insensitive to ethnic factors and that there are no significant relevant differences in extrinsic factors, including the practice of medicine, among the regions. The pharmacokinetics of the drug are insensitive to intrinsic and extrinsic factors. The diagnosis and therapy of the conditions in the indication do not significantly vary among regions. Nonetheless, the regulatory authority of the new region is requiring an additional study of safety and efficacy for bridging. Is this requirement inconsistent with E5?	No, although you might want to discuss the issue with the regulatory authorities in the new region. E5 makes it clear that the need for a bridging study is always a matter of judgment and does not seek to discourage the new region's asking for one. E5 specifically notes that familiarity with the other region is likely to be an important determinant of whether the new region asks for a bridging study. E5 does indicate the expectation that the regulatory authorities of new regions would request only those additional data necessary to assess the ability to extrapolate foreign data to the new region, but the amount of additional data called for is a matter of judgement on the part of the regulatory authority.
5	**Nov. 2003**	My drug has been approved in two ICH regions and I am about to meet with regulatory authorities in the third region to discuss an application for marketing. I believe that the new regulatory authority should accept the present data, and that regulatory authority should require little or no additional data. What information should I submit to support my case that additional data are not needed?	There are two distinct issues that need to be considered: 1) the adequacy of the data base and 2) the need for a bridging study. You will need to convince the regulatory authority that the available data are both adequate to meet the new region's requirements and that the data are applicable to the population of the new region. You should therefore indicate how your data address all the regulatory requirements of the new region. Where the choice of control groups, primary endpoints, or other key clinical trial design features are not those known to be considered acceptable to the new region, you should explain how and why they should be considered to meet the regulatory requirements of the new region. You should also indicate why the data and conclusions should be considered relevant to the new population. In doing this, you should identify the intrinsic factors (e.g. racial distribution) that differ between the regions and show that those factors do not substantially affect the drug effect (i.e. demonstrate that the drug is insensitive to any differences in ethnic factors). Data indicating that pharmacologically related compounds have similar effects in the two regions can be quite useful.

E5 Ethnic Factors : Questions and Answers

Date of Approval		Questions	Answers
			You should also identify the extrinsic factors (e.g. diagnosis or management of the patient population studied) that you believe are generally similar to those in the intended population in the new region and explain why any significant differences would not alter conclusions to be drawn about the drug effect. Dose-response relationships should be evaluated to determine if these are sensitive to intrinsic or extrinsic factors, and whether the appropriate doses might vary markedly among individuals or ethnic groups.
6	**Nov. 2003**	I believe that my drug is insensitive to ethnic factors and that drugs in its class have similar activity in all regions. However, the endpoints I studied and/or the control group I used were considered acceptable to the regions in which the studies were conducted but not to the new region. Does E5 indicate that the new region should accept those data as evidence of efficacy?	No. E5 indicates clearly that it applies only when the foreign clinical data address all the regulatory requirements of the new region, but come from a different region. E5 does not address the regulatory requirements of individual regions. If your choice of clinical endpoints or control group is not considered acceptable to the new region, and if you cannot convince regulators in that region otherwise, then E5 does not apply to this situation. Early discussion with regulators in regions where endpoints, control groups, inclusion criteria or diagnostic criteria might differ should be considered part of planning clinical studies to meet an individual region's requirements. In this situation, the regulatory authority in the new region may require you to conduct a study using agreed-upon criteria in the new region.
7	**Nov. 2003**	I believe my drug is insensitive to ethnic factors. However, there is a clear difference in medical practice and the use and perceived need for certain drugs in the targeted therapeutic area. Does E5 indicate that the new region should accept those data as evidence of efficacy?	No. As described, the data base might not be acceptable to the new region, apart from concerns about ethnic differences, because the data do not refer to a disease that the new region considers pertinent.
8	**Nov. 2003**	My drug has been shown to be effective in preventing certain clinical events. However, the rate of these events	No. Certainly, in most cases where there is a definitive outcome study in another region, a region would probably not require that the study be

E5 Ethnic Factors : Questions and Answers

Date of Approval		Questions	Answers
		is clearly different in the new region, even though the pathophysiology is the same. Does E5 indicate that the new region should accept those data as pivotal evidence of efficacy?	repeated locally. There could, however, be exceptions; for example, if the event rate is indeed lower in the new region, and the risk reduction is the same in both regions, the actual number of patients benefited will be smaller and an adverse effect could become more important, affecting the benefit to risk relationship of the drug. A new region, in some cases, might need a clinical trial to assess the value of the drug.
9	**Nov. 2003**	My drug is approved for various indications in one region and it is shown in a bridging study in the primary indication that the data can be extrapolated. Does this mean that the new regions should accept all indications without further data?	No. Whether or not the new region will require further data would be decided on a case-by-case basis, depending on whether the "bridged" indication was thought to satisfy all concerns about potential ethnic differences. For example, the additional indications might be extensions of the primary indication (perhaps not calling for an additional bridging study) or quite new uses (perhaps calling for bridging). It is recommended that early consultation and discussions be held with the authorities in the new region.
10	**Nov. 2003**	E5 expresses the principle that, as experience with interregional acceptance of foreign clinical data increases, there will be a better understanding of situations in which bridging studies are needed and that it is hoped that, with these experiences, the need for bridging data will lessen. Is this principle still valid?	Yes, this is the expectation. The accumulation of experience by each region with implementation of the E5 guidance continues to add to our understanding of situations in which a bridging study would be considered necessary by a new region. The expectation continues to be that, with this experience, the need for a bridging study will lessen.
11	**June 2006**	There seems to be an impression that the E5 bridging study would always be conducted after data in the original region is complete. Is this correct? It may be desirable in certain situations to achieve the goal of bridging by conducting a multi-regional trial under a common protocol that includes sufficient numbers of patients from each of multiple regions to reach a conclusion about the effect of the drug in all	Bridging data should allow for extrapolation of data from one region to another. Although E5 speaks generally to extrapolation of data to a new region, E5 was not intended to suggest that the bridging study should necessarily follow development in another region. In the answer to Q1, it is made clear that it is also possible to include earlier studies conducted in several regions in a global drug development program so that bridging data might become available sooner. This can expedite completion of a global clinical development program and facilitate registration in all regions. A bridging study therefore can be done at the beginning, during or at the end

E5 Ethnic Factors : Questions and Answers

Date of Approval		Questions	Answers
		regions. Please provide points to consider in designing, analyzing and evaluating such a multi-regional trial.	of a global development program. For a multi-regional trial to serve as a bridging study for a particular region, it would need to have persuasive results in that region, because it is these regional results that can convince the regulators in that region that the drug is effective, and can "bridge" the results of trials in other regions in the registration application. A multi-regional trial for the purpose of bridging could be conducted in the context of a global development program designed for near simultaneous world-wide registration. The objectives of such a study would be: 1) to show that the drug is effective in the region and 2) to compare the results of the study between the regions with the intent of establishing that the drug is not sensitive to ethnic factors. The primary endpoint(s) of the study should be defined and acceptable to the individual regions and data on all primary endpoints should be collected in all regions under a common protocol. In instances where the primary endpoints to be used by the regions are different, data for comparison purposes on all primary endpoints should be collected in all regions. For a study intended to serve as a bridging study, the following points should be considered: **Planning** The multi-regional trial would have to satisfy requirements of the region where the application is to be filed with respect to design and analysis (see answer to Q1). In general, a multi-regional study should be designed with sufficient numbers of subjects so that there is adequate power to have a reasonable likelihood of showing an effect in each region of interest. Minor differences in design (e.g., age inclusion criteria, concomitant medication, etc.) may be acceptable and prior discussion with regulatory agencies is encouraged. For safety evaluation, it is important to make as uniform as

Date of Approval	Questions	Answers
		possible the method for collection and assessment of safety information among regions. **Analysis** Given the goal of the multi-regional bridging study, it is critical to provide efficacy and safety results by region, with attention given to the usual analyses (e.g., demographic and baseline variables, patient disposition). It will be of interest also to examine consistency of effects across regions. In a dose response study, it will be especially important to analyze dose response relationships for efficacy and safety both within the regions and across the regions. **Evaluation** It is difficult to generalize about what study results would be judged persuasive, as this is clearly a regional determination, but a "hierarchy of persuasiveness" can be described. 1. Stand Alone Regional Result The most persuasive would be demonstration of the effect in the entire study, with the results of each region of interest also demonstrating a statistically significant result. It will also be important to compare results across regions. 2. No Significant Regional Result but Similar Results across Regions With an effect demonstrated in the entire study, an analysis of results by region might not show a significant result in a region of interest but the data might nonetheless be persuasive to regulators in that region. Consistent trends in endpoint(s) intended for comparison across the regions or, in the case of a dose-response study, similar dose-response relationships across

E5 Ethnic Factors : Questions and Answers

Date of Approval		Questions	Answers
			regions, might support an argument that the drug is not sensitive to intrinsic or extrinsic ethnic factors. Other data, for example, from approved drugs in the same class within region(s) could support such a bridging conclusion. **Other consideration** This Q & A discusses use of multi-regional studies as bridging studies. There are other possible uses of multi-regional studies. For example, at an early stage of development, such studies could compare various endpoints in an exploratory setting in different regions to guide a synchronized global development plan.

FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Meeting of the Psychopharmacologic Drugs Advisory Committee

September 16, 2010

Alkermes, Inc. submitted a supplemental New Drug Application for VIVITROL seeking an indication of treatment of opioid dependence. In support of this indication, the applicant has submitted the results of a single placebo-controlled efficacy trial. VIVITROL is currently labeled for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with VIVITROL.

This committee will discuss whether the data support an indication for the prevention of relapse in detoxified opioid dependent patients.

Discussion Points for the Committee

1. Discuss whether the available efficacy data taken together with pharmacodynamic data are sufficient to conclude that the drug is effective for the intended use.

2. Discuss whether the differences between the studied population and the American target population creates a need for a "bridging study" of some type to provide assurance that the drug would be effective in the American population.

3. Discuss whether there are indication-specific safety concerns that have not been adequately addressed by the existing safety data, and whether additional safety data may be needed in the American population.